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HEALTH EFFECTS OF ALPHA-EMITTING PARTICLES IN THE RESPIRATORY TRACT

Report of Ad Hoc Committee on
"Hot Particles" of the Advisory Committee
on the Biological Effects of Ionizing Radiations

National Academy of Sciences
National Research Council

OFFICE OF RADIATION PROGRAMS
U. S. ENVIRONMENTAL PROTECTION AGENCY

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16. Abstracts

The report presents a summary and analysis of current knowledge concerning health effects of alpha-emitting particles in the respiratory tract. The findings of the Committee were: 1) Lung cancer mortality in experimental animals can be adequately accounted for by averaging the absorbed alpha radiation dose over the entire lung; 2) Human data suggests the radiocarcinogenic sensitivity of the tracheobronchial region of the lung is greater than that of the alveolar region and the cancer risk for alpha irradiation of the alveolar region would not be underestimated by using the risk factors obtained for the tracheobronchial region; 3) Experimental evidence suggests the carcinogenic response is more a function of the amount of radioactivity in the lung than its distribution.

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October 1976

NATIONAL ACADEMY OF SCIENCES
NATIONAL RESEARCH COUNCIL
Washington, D.C. 20006

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NOTICE

The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the Councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the Committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

The work presented in this report was supported by the Office of Radiation Programs, Environmental Protection Agency, under Contract No. 68-01-2230, Modification Nos. 2 and 5.

FOREWORD

In the summer of 1974, the Environmental Protection Agency asked the National Academy of Sciences for information and evaluation of the health effects of alpha-emitting particles ("hot particles") in the respiratory tract. This report was prepared in response to that request.

The report presents a summary and analysis of current knowledge concerning health effects of alpha-emitting particles in the respiratory tract. The report also reponds to the questions raised by Drs. T. B. Cochran and A. R. Tamplin of the Natural Resources Defense Council about the adequacy of presently existing standards for "hot particles."

We want to thank the several people who helped in preparation of this report and who have contributed material for consideration by the Committee. We particularly want to thank Ms. Leila Counts, Editor, Battelle, Pacific Northwest Laboratories, who assisted in the preparation of the final report.

PREFACE

This analysis of the cancer hazard to the lung from inhaled plutonium particles was done under the auspices of the National Academy of Sciences (NAS) at the request of the Environmental Protection Agency (EPA). The report defines the overall problem, describes its historical background, and summarizes relevant current knowledge. Supporting documentation is included as Appendix A.

The Committee has endeavored to ensure that no sources of pertinent knowledge or expertise were overlooked in its study. During the course of its deliberations, the Committee solicited the opinions and counsel of several individual scientists and others with information needed for a complete overview of the problem.

Of special note is that the Committee met with Drs. T. B. Cochran and A. R. Tamplin to specifically receive their views and to discuss these views with them. A complete transcript of this meeting is part of the NRC/NAS file of the Committee.

Appendix B describes the procedure used to select the Committee and gives biographical data about Committee members. A listing of all meetings held and the participants is given in Appendix C. Complete documentation, including working papers used to prepare the report, is in the NRC/NAS files.

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*After the Committee had completed the study and formulated its conclusions but before the final draft of the manuscript was complete, Chairman Albert assumed a post with the Environmental Protection Agency. Although he remained a member of the Committee, Dr. Albert thereafter limited his participation in the Committee's activities. The Committee then asked Drs. Bair, Alpen, and Lewis to assume responsibility for the task of incorporating into the final manuscript the Committee's responses to the suggestions of external reviewers. The entire Committee reviewed and assumes responsibility for the final manuscript.

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HEALTH EFFECTS OF ALPHA-EMITTING PARTICLES IN THE RESPIRATORY TRACT

SUMMARY AND CONCLUSIONS

Since the early 1950's, various groups with responsibility for determining the effects of radiation sources on human health have recognized the possibility that radioactive material deposited in tissues of the body as high specific activity particles might be a greater health hazard than the same source distributed more homogeneously. This has been referred to as the "hot particle" problem [1-5].

In 1974 Cochran and Tamplin hypothesized that the intense and highly localized dose from inhaled insoluble plutonium particles larger than a specified size causes greater tissue damage, and is therefore more carcinogenic, than more uniformly-delivered irradiation [6]. On this basis Cochran and Tamplin advocated a 115,000-fold reduction in the current radiation standards governing exposure to insoluble alpha-emitting ("hot") particles. With the support of the 1974 Cochran and Tamplin report, the Natural Resources Defense Council (NRDC) petitioned the Environmental Protection Agency (EPA) to reduce the current radiation protection guides accordingly.

The National Academy of Sciences-National Research Council Ad Hoc Committee on "Hot Particles" has concluded that the evidence does not support the NRDC petition for a special, lower radiation protection standard for inhaled alpha-emitting particles. The current state of knowledge about the "hot particle" problem can be summarized as follows:

1. In animals, all experimental data so far obtained indicate that when insoluble plutonium particles are inhaled, the major radiation dose in the lungs occurs in the pulmonary (i.e., alveolar) region. The principal delayed effect in the lung of breathing these particles is induction of alveolar cancers. An analysis of mortality from these cancers in beagle dogs indicates that if there is a hot-particle effect, Cochran and Tamplin have overestimated the cancer risk per particle by at least two orders of magnitude. However, analyses indicate that the observed lung cancer mortality in these dogs can be adequately accounted for by the conventional method of averaging the absorbed alpha radiation dose over the entire lung. Therefore, it is concluded that if there is a "hot particle" risk, it is small by comparison with the lung cancer risk attributable to the generalized alpha radiation.

2. In human beings, epidemiological evidence gained from experience with inhalation of alpha-emitting radon daughters and with external X or gamma irradiation of the thorax strongly suggests that the radiocarcinogenic sensitivity of the tracheobronchial region is greater than that of the alveolar regions where inhaled plutonium is retained. Therefore, we would not expect the human cancer risk from alpha irradiation of the deep lung tissues to be underestimated by applying risk factors obtained from human experience with cancer induced by irradiation of the lining of the bronchial tree.

3. Current evidence indicates that the cancer hazard from insoluble particulate plutonium deposited in the lungs is not markedly greater than would be caused by the same quantity of radioactivity distributed more uniformly. The experimental evidence suggests that the carcinogenic response is more a function of the **amount** of radioactivity in the lung than of its distribution.

DEFINITION OF THE PROBLEM

In its simplest terms, the question addressed by the Committee is: Does an insoluble, highly radioactive particle small enough to be taken into body tissues, especially the lung tissues, have a greater probability of producing a significant biological effect, such as cancer induction, than does an internal source of radiation of equivalent physical dose which is distributed more uniformly?

Although the issue of the hazard from non-uniform distribution of radioactive particles is pertinent to all types of radiation, it is most relevant to alpha radiation from the transuranic elements, such as plutonium, americium, and curium. Particles containing these elements irradiate small regions around themselves, extending not more than 50 μm in solid tissues and about 200 μm in the alveolar tissues of the lungs. Moreover, many of these transuranic elements have long half-lives and form highly insoluble oxides which may persist in tissues for long periods, even years. Local doses from discrete small sources can reach very high values, even when the computed mean tissue dose in the organ is very low. Under these conditions, the concept of dose as generally used in radiation protection is not applicable. The energy from a single alpha decay event, with its short and well-defined range, will be absorbed by one or, at most, several cells, which may be killed or severely damaged. Other cells, not actually traversed by alphas, will suffer no direct alpha radiation injury.

Although insoluble particles move about within the lungs as a result of cellular and other clearance processes, it is not known how rapidly or freely the particles move. Since the degree to which insoluble particles move about in the lungs is unknown, the distribution of radiation dose within the lungs is uncertain, but it probably varies from nearly uniform to highly localized, depending upon the physical properties of the particles and the degree of cellular interaction with the particles. The "hot particle" issue arises from the possibility that there might be no movement, or relatively slow movement, of high specific activity particles within the lungs.

Although radioactive particles may enter the body through the integument or the intestinal wall, the principal concern in this report is with inhaled particles. This is so because inhalation is likely to be a principal source of exposure and because respiratory tissues are particularly vulnerable to radioactive particles, being directly exposed to airborne material with immediate direct contact between particles and cells. In this report, therefore, the hot particle problem is considered in relation to the respiratory tract only. However, this discussion could apply to any tissue where particles may be translocated and retained for a significant time.

In preparing this report the Committee drew upon all relevant published data and the current experience of nearly all laboratories throughout the world doing research on this problem. The data base used by the Committee was far broader than that upon which the Cochran-Tamplin rationale was developed.

HISTORICAL BACKGROUND

During the early stages of the development of radiation biology from a descriptive to a quantitative science, one of the first problems to emerge was that of predicting the effects of radiation exposure delivered in a nonuniform manner. An early attempt to account for the nonhomogeneous distribution of radioactive substances deposited in body tissues was the concept of "critical organ," as explicitly stated in National Council on Radiation Protection and Measurements (NCRP) Handbook 52 (1953) [1] and in International Commission on Radiological Protection (ICRP) recommendations (1955) [2]. The critical organ concept assumes that different organs vary in uptake of radionuclides and radiosensitivity. It also assumes that the radionuclides are deposited uniformly throughout the organ.

However, early NCRP and ICRP reports recognized that for certain radionuclides the dose may not be homogeneously deposited in critical organs (NCRP Handbooks 52 [1953] [1] and 69 [1959] [3]). In 1961 the particulate source problem was noted explicitly by the NAS/NRC Subcommittee on Inhalation Hazards of the Committee on Pathologic Effects of Atomic Radiation [4]. The Subcommittee considered the issue of whether "mean dose to the lung" is relevant when the source is particulate and nonuniformly distributed. This of course involves the distinction between the microscopic dose in the paths of the ionizing particles and the macroscopic dose which results from averaging such events over the whole organ. The Subcommittee also recognized the possibility that radioactive material deposited as high specific activity particles might be more damaging to tissue than the same source homogeneously distributed. The Subcommittee referred to the work of Passoneau [7], which indicated that the carcinogenic potential for ^{90}Sr-^{90}Y was lower when the activity was in high specific activity beads. This model, which was based on beta-emitting isotopes and tumor production in rat skin, may not be relevant to the case of much smaller alpha-emitting particles in lung tissue.

In 1969, the International Commission on Radiological Protection (ICRP) [5] defined three categories for nonhomogeneous exposure to ionizing radiation: **Class 1** (Partial Irradiation of Representative Tissue) - in which the part irradiated is representative of the whole organ or tissue, as in external irradiation of skin or bone marrow; **Class 2** (Partial Irradiation of Nonrepresentative Tissue) - in which the part irradiated is not representative of the whole; and **Class 3** (Irradiation from Radioactive Materials in Particulate Form) - which includes irradiation from discrete particles containing radionuclides or from a highly focal accumulation of radionuclides.

Again in 1972, the Committee on Biological Effects of Ionizing Radiation (NAS/NRC) in their report [8] raised the issue of "hot spots", or particulate sources, as inducers of lung cancer. The BEIR Committee referred to the work of Grossman et al. [9], who compared the carcinogenicity of ^{210}Po in the lung when the agent was administered by intratracheal instillation with and without a particulate carrier. Grossman et al. concluded that tumor production was a function of total alpha dose, whether the isotope was given with or without a particulate carrier. The inference drawn by the BEIR Committee was that "a higher localized dose from alpha particles was not more cancerogenic than the same mean tissue dose delivered more uniformly to critical cells" [8]. However, the biological effects of intratracheally instilled polonium, which has a relatively short half life (138 days), may be quite different from those of inhaled insoluble particles of plutonium, which has a much longer half life.

In November of 1974 a report was published by Cochran and Tamplin [6] in support of a petition made by the Natural Resources Defense Council to the Environmental Protection Agency and the Atomic Energy Commission. The petition requested a reduction in the current radiation standards governing the internal exposure of man to insoluble alpha-emitting particles. The authors reviewed certain existing data on carcinogenesis from point sources of alpha radiation and drew on selected published biological experiments to conclude that the radiation protection guides should be reduced by a factor of about 115,000.

Following publication of the Cochran and Tamplin report, the question of alpha-emitting particles in the lungs was addressed by Bair, Richmond, and Wachholz [10], the British Medical Research Council [11], the National Council on Radiation Protection and Measurements [12], and the National Radiological Protection Board in the United Kingdom [13]. All of these sources have concluded that there is no evidence that the risk of lung cancer from alpha-emitting particles in the lungs is greater than from equivalent amounts of alpha radiation more uniformly distributed. They also agreed that there is no compelling reason to abandon the average lung dose convention for radiation protection practices, which is the same convention currently used to quantify the radiation doses associated with plutonium-induced lung cancer in experimental animals. However, Cochran and Tamplin did not accept these reports as refutation of their "hot particle thesis" [14].

THE COCHRAN-TAMPLIN RATIONALE AS A BASIS FOR THE NRDC PETITION

As Cochran and Tamplin noted in their 1974 report [6], the current ICRP occupational exposure standard for insoluble plutonium in air is 4×10^{-11} μCi/mℓ. This level of atmospheric contamination would lead to a maximum permissible lung burden (MPLB) of 0.016 μCi and would be associated with a maximum permissible lung dose of 15 rem/yr, averaged over the entire lung.

Cochran and Tamplin [6] pointed out that in the case of insoluble plutonium particles, the dose is not delivered uniformly to the entire lung:

> It would take 53,000 particles . . . (1 μ in diameter, 0.28 pCi) . . . to reach the MPLB of 0.016 μCi which results in 15 rem/yr to the entire (1000 g) lung. However . . these particles would irradiate only 3.4 g of this 1000 g to the lung, but at a dose rate of 4000 rem/yr . . . these particles result in an intense but highly localized irradiation. A fundamental question is, then: is this intense but localized irradiation more or less carcinogenic than uniform irradiation?

The Cochran-Tamplin approach to predicting the cancer risk from hot particles is based on the Geesaman Hypothesis [15,16], which in turn is based almost wholly on the rat skin irradiation experiments of Albert and his coworkers [17-20]. Cochran and Tamplin's interpretation of these experiments and the rationale for their proposed standard are described by the following excerpts from their 1974 report [6]:

> A high incidence of cancer was observed after intense local doses of radiation, and the carcinogenesis was proportional to the damage or disordering of a critical architectural unit of the tissue, the hair follicles. (Page 23)

> Certainly a reasonable interpretation of these experimental results is: when a critical architectural unit of a tissue (e.g., a hair follicle) is irradiated at a sufficiently high dosage, the chance of it becoming cancerous is approximately 10^{-3} to 10^{-4}. This has become known as the Geesaman hypothesis. (Page 26)

> Geesaman indicates that the tissue repair time in the lung is on the order of one year. It therefore seems appropriate, but not necessarily conservative, to accept as guidance that this enhanced cancer risk occurs when particles irradiate the surrounding lung tissue at a dose rate of 1000 rem/yr or more. (Page 33)

> . . . using Geesaman's lung model, a particle with an alpha activity between 0.02 pCi and 0.14 pCi is required to give a dose of 1000 rem/yr to irradiated lung tissue. For purposes of establishing a maximum permissible lung particle burden we will use 0.07 pCi from long half-lived (greater than one year) isotopes as the limiting alpha activity to qualify as a hot particle. (Page 34)

The existing standards for uniform radiation exposure of the whole body or lung can be used as the basis for establishing particle exposure standards by equating the risk of cancer induction between the two types of exposure (uniform versus grossly nonuniform). The most recent assessment of the risk associated with uniform irradiation of man was performed by the NAS-NRC Advisory Committee on the Biological Effects of Ionizing Radiation. Their report, published in 1972, is referred to as the

> BEIR Report . . . the existing occupational exposure standard for uniform whole body irradiation is 5 rem/yr and for the lung, 15 rem/yr. The BEIR Report estimates that exposure of the whole body of an individual to 5 rem/yr would lead to a cancer risk between 4.5 x 10^{-4} and 2.3 x 10^{-3}/yr. Their best estimate is 10^{-3}/yr. (Pages 41-42)
>
> It is recommended here that the best estimate of the effects of uniform exposure by the BEIR Committee be used together with a risk of cancer induction of 1/2000 per hot particle in determining the MPLPB for insoluble alpha-emitting radionuclides in hot particles. This is a somewhat arbitrary compromise and is not the most conservative value that could be recommended. Thus, the recommended MPLPB for occupational exposure from hot particles of alpha-emitting radionuclides in the deep respiratory zone is 2 particles. This corresponds to a MPLB of 0.14 pCi and represents a reduction of 115,000 in the existing MPLB. (Pages 43-44)

In February 1975, in a supplemental submission [21] to the Environmental Protection Agency's Public Hearing on Plutonium and the Transuranium Elements, Cochran and Tamplin added to their definition of a "hot particle:"

> In our petition and Hot Particle Report, we concluded that, consistent with the whole body exposure standard of 5 rem/year, the alpha-emitting hot particle standard should be 2 particles in the human lung. Using the estimated minimum hot particle activity of 0.07 pCi, this resulted in the suggested reduction of the MPLB by 115,000. However, as we stated in our Hot Particle Report, this factor of 115,000 would apply only when it was not determined that the activity was not on hot particles. Using the particle size distribution determined for the Rocky Flats fire, and allowing only 2 particles above 0.07 pCi would still have required a reduction of the MPLB by a factor of 16,000. (Page 22)

Based on their development of particle size statistics for the exposure of personnel at the time of the plutonium facility fire at Rocky Flats, Colorado, Cochran and Tamplin "see little justification for selecting a minimum hot particle activity greater than 0.6 pCi/particle . . . a 2-particle limit at 0.6 pCi/particle would still require a reduction of the MPLB by a factor approaching 2000." (Pages 22 and 24) [21].

A CRITIQUE OF THE COCHRAN-TAMPLIN PROPOSAL

The Committee views the Cochran-Tamplin thesis as based on three assumptions. Assumptions 1 and 2 together form the Geesaman Hypothesis and Assumption 3 is the Hot Particle Hypothesis. The assumptions are described and commented on below.

Assumption 1

The correlation between the induction of atrophic hair follicles and the induction of tumors in rat skin with ionizing radiation [17-20] is assumed by Cochran and Tamplin to indicate that the atrophic hair follicle causes the skin tumors and that the role of ionizing radiation is only to produce the structural damage to the hair follicles.

Comment

Atrophic follicles are structures which have lost the ability to produce hair, for any of a number of reasons. When radiation is involved in atrophy, however, the atrophy results from the radiation-induced death of the hair germ cells, which are the stem cells for hair production normally found at the base of the resting hair follicles. The most likely explanation for the association between follicle atrophy and tumor induction is that ionizing radiation causes concomitant cell death and neoplastic cell transformation.

It is a generally established concept in the etiology of cancer that the disease is initiated by the neoplastic transformation of single cells. The transformation of single cells by carcinogens can be shown in tissue culture studies, where it is evident that cell lethality and cell transformation are concurrent effects. However, the dose-response relationships for the two effects vary sufficiently to indicate that the processes are independent. It has been shown that carcinogen-induced cell death can be prevented without affecting the yield of transformed cells [22]. And, while tissue damage is commonly seen in association with cancer formation, there is strong evidence that the two effects represent different aspects of carcinogenic action.

Assumption 2

Geesaman [15,16] generalized (Assumption 1) that follicle atrophy causes skin tumors in the rat. He expanded this assumption to conclude (as Assumption 2) that the probability of cancer due to focal tissue damage in the lung caused by a microscopic plutonium particle will be 1/2000, which is the hypothesized ratio of tumors-to-atrophic follicles in the rat skin.

Comment

This Geesaman Hypothesis, on which the Cochran-Tamplin proposal is based, revives one of the oldest cancer theories; namely, that the cause of cancer is chronic tissue damage. This is the chronic irritation theory propounded by Virchow in 1863. The theory, as reviewed by Oberling [23], was in vogue for about 50 years. It stemmed from the early clinical observations that cancer rarely appears in healthy tissue and is almost always preceded by chronic inflammatory conditions such as scars, ulcerations or fistulas. Postmortem observations in this era suggested that the same association applies to internal organs.

Virchow pointed out that every injury to tissues is followed by a state of irritation in which the cells are stimulated to multiply in order to repair the damage. If the injurious conditions prolong the irritation, the cell proliferation grows more and more excessive and irregular. Virchow argued that if such a condition persists year after year, cancer will occur.

The Virchow theory claimed that chronic irritation was the sole, nonspecific cause of cancer: i.e., that cancer was the outcome of many widely differing conditions with no features in common except chronic damage.

As related by Berenblum [24], Virchow's theory was eventually demolished. Experiments begun in 1918 showed that cancer can be produced by some potent substances that vary widely in their capacity to cause damage; on the other hand, many agents which cause substantial damage were shown not to cause cancer.

Regarding radiation, analysis of the data on induction of skin tumors in rats by alpha rays [17-20] indicates that nearly all of the potentially dividing cells (>99.9%) in each hair follicle were sterilized by even the lowest dose used. This means that increasing the dose will produce only a negligible increase in the number of destroyed cells. Since the number of tumors increased very much more rapidly with dose, these data negate the assumption that follicle atrophy (or a nidus of dead cells) is the only cause of tumor formation in rat skin.

Assumption 3

On the basis of Assumption 2, Tamplin extends the Geesaman Hypothesis to make Assumption 3: when the dose to the surrounding tissue from the alpha-emitting particle exceeds 1000 rad/yr, focal damage will be produced with a cancer risk of 1/2000. This is the Hot Particle Hypothesis.

Comment

It is stated that 1000 rad/yr was selected as the critical dose at which cancer risk from ionizing radiation could be quantitatively assessed in man because this dose is the minimum that produces cancer in the rat skin and lung, and the life span of lung cells is normally about one year. However, the logic of this reasoning is obscure because no systematic relationships are known to exist between the rate of cell turnover and tissue damage by alpha radiation in the lung or any other organ. The selection of parameters appears to have been arbitrary.

SUMMARY EVALUATION OF THE COCHRAN-TAMPLIN RATIONALE

The exposure pattern in the deep lung to insoluble alpha-emitting particles always involves focal irradiation. Particles deposited in the alveoli are transported through the lymphatics and concentrated around the respiratory and terminal bronchioles [25]. Hence, the problem for insoluble particles does not represent a comparison of uniform and focal exposures, but a comparison of the relative effects of greater numbers of small particles compared to smaller numbers of large particles for the same total lung burden.

Radiobiologic theory supports the concept that for respirable-sized particles distributed in a tissue, the number of cells traversed by alpha radiation, and probably also the carcinogenic risk, increases with increasing particle size or particle activity and reaches a maximum at a given particle size or particle activity. At particle sizes or particle activities above this maximum the probability of multiple traversals of single cells increases, thus increasing lethality. This results in a reduced carcinogenic risk since dead cells cannot become cancer cells [12,26].

On the other hand, radiobiologic theory also supports the concept that if the alpha activity is distributed throughout the tissue, the number of cells that receive only single traversals or sublethal events of some nature increases with the amount of alpha-emitters present in the lungs and the cancer risk increases similarly. Of course, at very high concentrations of alpha-emitters the number of cells receiving multiple traversals increases and the risk of radiation pneumonitis and fibrosis becomes more significant, while the cancer risk decreases. Experimental efforts to verify these concepts are continuing, but results to date do not contradict this description [27].

In experimental animals the carcinogenic risk is reasonably independent of the geometric distribution of the particles in the lungs. In a complex organ like the lung it is possible that particle size may affect the distribution, and hence the risks, among various tissues. However, experimental evidence suggests that because of competing tendencies in this distribution, the overall tumorigenic response for a variety of particle sizes is a function of the total radioactive dose involved and is relatively insensitive to differences in the distribution in various tissues.

The Geesaman Hypothesis, on which the Cochran-Tamplin rationale is based, has merit only to the extent that tissue damage which results in permanent structural disorganization can have an enhancing effect on the tumorigenic response to carcinogen exposure. The postulate that structural disorganization, per se, produces tumors has been shown to be true only in the endocrine system where hormonal feedback-regulating mechanisms operate from one organ to another (e.g., the ovary and pituitary glands). Under these circumstances gross destruction of organs (not microscopic focal derangements) can be a condition for a tumorigenic response.

Geesaman's postulate, that the damage produced in the lung by a single plutonium particle would have the same probability of causing lung cancer as that observed in the irradiated rat skin, makes the following unwarranted assumptions about the pathogenesis of radiation-induced tumors in the rat skin: a) that atrophic follicles, per se, cause skin tumors (i.e., that structural disorganization of this type is tumorigenic) at a relatively low probability of 1 in 2,000; and b) that focal irradiation of hair follicles, as would occur from stationary plutonium particles adjacent to hair follicles, causes atrophic follicles and skin tumors. Since the Geesaman Hypothesis could hardly be taken as the basis for predicting the yield of tumors, even in the rat skin, from imbedded plutonium particles, it would be purely fortuitous if it accurately predicted the response of the human lung to plutonium particles. Therefore, the rationale for the NRDC petition appears indefensible.

CURRENT STATUS OF THE RADIATION BIOLOGY OF INHALED ALPHA-EMITTERS*

The potential health effects caused by inhalation of alpha-emitting radioactive particles depend on the properties of the particles. Particles released from the nuclear fuel cycle may vary widely in radionuclide content, from low specific activity particles (largely of uranium) to high specific activity particles of nearly pure plutonium, curium or americium. The particles may contain beta and gamma-emitting radionuclides in addition to the alpha-emitting transuranics. Other particle properties (such as chemical composition, density, and size) can also vary over a wide range, depending upon the mode of formation and the route of release.

Only in extraordinary circumstances would human beings be exposed to particles of a fairly homogeneous size distribution (such as pure plutonium oxide particles). Accidental exposures would be to aerosols comprised of randomly shaped particles with a variety of physical and chemical properties and a wide variation in sizes [28,29]. The particles would most likely contain mixtures of uranium, transuranic elements and fission products. Thus, it is very difficult to assess the health effects that could result from such an exposure.

FACTORS IN DOSE-RESPONSE RELATIONSHIPS

Variations in anatomical and physiological properties of the respiratory tract increase the complexity of assessing the potential health effects of exposures to aerosols containing transuranic elements [30-35]. These differences, compounded by respiratory diseases, exposures to other sources of radiation and nonradioactive toxic substances, and differences in physical activity and (possibly) genetic constitution among individuals, influence susceptibility to the biological effects, including lung cancer, of inhaled transuranic elements. Furthermore, since data on the effects of transuranic elements in human lungs are lacking, the assessment of potential health effects depends largely on the results of animal experiments.

Fate of Inhaled Particles

The chemical and physical properties of inhaled alpha-emitting particles and their deposition sites in the respiratory tract determine the eventual fate of particles in the lung and subsequent biological effects. Clearance of particles deposited in the respiratory tract occurs through the gastrointestinal tract, through the lymphatic system or by dissolution and absorption into the blood. Clearance from the upper respiratory tract is very rapid, within a few hours, but clearance from the lower respiratory tract and the alveolar region may require weeks or even years. Particles are cleared from the nasal regions to the external environment or to the gastrointestinal tract within the first hours after inhalation [36]. The process may be accelerated by sneezing and other mechanical functions. Since absorption of transuranics from particles in the gastrointestinal tract is usually much less than 0.1% [37], nearly all particles cleared from the respiratory passages to the gastrointestinal tract are excreted.

Particles deposited in the tracheobronchial region of the lungs are transported in the layer of mucus, propelled by ciliary action toward the esophagus. Interpretation of experimentally-determined clearance curves indicates that plutonium oxide particles are probably cleared from the tracheobronchial region with a half-time of up to about 3 days [38].

Particles deposited in the alveolar region may be cleared by dissolution and absorption into the blood, by mucociliary action through the tracheobronchial tree, or by transport via the lymphatic system. The relative importance of each pathway for given particles depends upon many factors, such as the particles' chemical and physical properties, specific activity, cytotoxicity, and the state of health of the respiratory tract. Estimates of the retention half-time of plutonium in the lungs of human beings accidentally exposed to plutonium aerosols range from about 300 to 650 days [39]. The ICRP recommends that the value of 500 days be used for radiation protection purposes [40].

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*More detailed supporting discussions are included in Appendix A.

Cigarette smoking has been reported to inhibit ciliary activity of the respiratory tract, which is an important mechanism for clearance of particles from the lungs [41]. This raises the question of whether plutonium would be retained in the lungs of smokers to a greater extent than in the lungs of nonsmokers. Slowing of mucus flow along the major bronchi, where movement is normally very rapid, does occur in human smokers [42]. However, no significant effects have been observed, in human beings free of bronchitis, on mucus transport in the smaller bronchi where movement is normally very slow [43]. There are no data relating the effects of cigarette smoking to clearance of particles from the human alveolar region. There also is no information available on residence times of particles deposited in areas of the bronchial mucosa which have been denuded of cilia, particularly the bifurcations of the bronchi. However, a recent report gives preliminary evidence for long-term residence of ^{210}Pb on the bronchial epithelium of cigarette smokers [44]. How this might relate to inhaled plutonium particles is not known.

Particles are cleared from the lungs to regional lymph nodes via the lymphatic vessels, probably those adjacent to bronchioles and bronchi. In experimental animals plutonium particles have been identified in lymphatic vessels beneath the pleural surface [25]. Evidence from experimental animals and from human beings accidentally exposed to plutonium indicates that plutonium particles accumulate and are largely retained in the lymph nodes. Thus, plutonium concentrations in lymph nodes are usually several times greater than those in lungs. However, lymphatic tissues have not been the site of primary cancers in experimental animals that inhaled plutonium [45].

Physics of Energy Absorption

Heavy ions, such as alpha particles, lose energy rapidly and produce a dense column of ionization as they penetrate cells and tissues. Because of this high rate of energy loss, their range in cells and tissues is short. A 5.3 MeV alpha particle emitted from plutonium has a range in water of about 41 μm with an average ion density of about 3500 ion pairs/μm. Due to slowing of the alpha particle, the ion density increases by about a factor of 2 at the end of its range. Thus, compared with electrons, energy from alpha particles is deposited in cells and tissues in a highly concentrated manner. An alpha particle which traverses the nucleus of a cell deposits more than enough energy, by several orders of magnitude, to destroy the cell's reproductive capability. Traversal through the cytoplasm, however, can damage the cell but leave its reproductive capacity unimpaired [46]. Therefore, when dealing with the biological effects of alpha irradiation, it is appropriate to consider the probability that a cell, especially the nucleus, might be traversed by an alpha particle, rather than the amount of energy (usually expressed in rad) deposited per unit mass of cells.

Calculations of the probability of epithelial cells in the lung being traversed by alphas emitted from plutonium particles lead to the conclusion that the number of cells killed or affected by such particulate sources will reach a maximum after a relatively short interval, regardless of the total activity involved, because a single traversal of a cell nucleus by an alpha particle should be sufficient to kill or affect the cell [25,26]. Thus, the probability that plutonium particles will induce a lung cancer is more likely to depend on the number of particles than on the specific activity of the particles. This supports the hypothesis that greater tumorigenicity per unit of absorbed dose results as the plutonium is more widely distributed throughout the lungs in smaller particles.

Cellular and Subcellular Effects

Knowledge of the mechanisms by which cancer is induced by alpha irradiation would help to resolve questions about the relative hazards of inhaled alpha-emitting particles of different sizes and specific activities. Unfortunately, most of our knowledge about the action of alpha irradiation at the cellular and subcellular levels concerns cell mortality, rather than cell transformation. Nevertheless, since the physical processes leading to alpha-induced cell transformation can be assumed to be similar to those related to cell death, data obtained from studies of cell mortality and chromosomal aberration can be useful in examining questions of spatial distribution of alpha dose and carcinogenesis.

These data suggest that single alpha particles that traverse the cytoplasm of a cell will have minimal, if any, impact on the cell's ability to survive and reproduce. Theoretical deductions, supported by studies of cells in tissue cultures, indicate that when a single alpha particle traverses a cell nucleus, it causes sufficient irreparable molecular damage to destroy the cell's reproductive capability [47,48]. These killed cells do not become cancers. When a cell nucleus receives only a portion of the energy from an alpha traversal and survives, the cell may retain its reproductive capability and pass on to its progeny certain genetic alterations which may have a bearing on subsequent events leading to cancer induction.

Brooks et al. [49] studied the frequency of chromosomal aberrations in the livers of Chinese hamsters following injection of ^{239}Pu citrate or $^{239}PuO_2$ particles of various sizes and numbers. The dose-response curves for aberrations per cell were similar for low total doses of ^{239}Pu particles and uniformly distributed ^{239}Pu. However, with ^{239}Pu particles a large portion of the aberrations occurred in a few cells that were considered by Brooks to be reproductively dead. Brooks et al. concluded that the ^{239}Pu particles posed a lesser hazard than did the more uniformly distributed ^{239}Pu. Insofar as cell death and chromosomal aberrations are related to cancer risk, the data suggest that the more uniform the distribution of the alpha flux, the greater the radiation effect.

Mechanisms of Carcinogenesis

Because the basic mechanisms of carcinogenesis are still essentially unknown, a discussion of this subject can give little insight into the hot particle problem. It is recognized, however, that the efficiency of carcinogenic action depends upon the carcinogen reaching biological targets within cells, the susceptibility of cells to transformation, and the extent to which transformed cells acquire properties of neoplasia, including unrestrained proliferation, invasiveness, and antigenicity.

The progeny of transformed cells have a variety of neoplastic and non-neoplastic characteristics; therefore, not all transformed cells lead to tumor formation. In addition, selection processes breed out some aberrant races of cells and other transformed cells die naturally (although this could conceivably facilitate the election process for tumor cells).

Within the present insufficient body of knowledge about carcinogenic processes and tumor biology, the concept of "precancerous lesions" has developed. Precancerous lesions are those which may precede and may favor the development of cancer but do not possess the essential elements of the disease [50]. However, although most so-called precancerous lesions have some neoplastic properties, such as cell proliferation and distortion, it is impossible to predict whether they will in fact develop into cancer. Tumor induction is the result of a series of critical events which are still imperfectly understood. The terms precancerous, pre-adenoma, etc. are used to indicate changes reminiscent of those preceding or concomitant with tumor development, but they do not have precise scientific meanings.

ANIMAL EXPERIMENTS

Animal experiments [51,52] have shown two responses at low levels of inhaled PuO_2: a reduction in the number of circulating lymphocytes and induction of lung cancer. Lung cancer, the long-term consequence of greatest concern, has been demonstrated in mice, rats, dogs, and baboons. Although studies are limited and still in progress, hamsters appear to be less susceptible to induction of lung cancer by inhaled plutonium than rats or dogs.

In all the animal experiments with inhaled transuranic elements, bronchiolo-alveolar carcinoma, a variant of adenocarcinoma, is the predominant resulting cancer type. The tumors appear to originate in the periphery of the lungs where, according to autoradiographic evidence, the main portion of the radiation dose is delivered.

In studies of inhaled plutonium it has been the general practice to relate biological effects to the total radiation doses delivered to the lungs. The doses are calculated on the basis that the deposited energy is absorbed by the total lung mass, including the blood. Although it has always been recognized that absorption of alpha radiation energy emitted by plutonium particles is not uniform, the actual distribution of the absorbed energy has not been well enough known to develop a more defensible practice. On the positive side, there is merit in using the same method for calculating dose in animal experiments as is used in setting standards for human exposure.

Animal experiments with inhaled plutonium have involved both relatively soluble and insoluble compounds. However, it should be recognized that although both soluble and insoluble compounds are deposited uniformly throughout the lungs after inhalation, both tend to become localized in "hot spots" as a result of cellular action and other processes acting to remove the foreign material. Soluble plutonium compounds are removed from the lungs more rapidly than insoluble compounds, mostly by absorption into the blood. The portion of soluble plutonium retained in the lungs continues to be localized for long periods of time. Even so, soluble plutonium compounds are distributed more widely than insoluble plutonium oxide particles and it is reasonable to believe that the absorbed radiation is also more widely distributed. Thus, it is difficult, if not impossible, to compare experimentally the effects of completely uniformly-distributed alpha irradiation with irradiation from particulate sources. It is possible, however, to perform experiments comparing more-uniform with less-uniform irradiation, or more-particulate with less-particulate irradiation. Experiments have been completed which allow these kinds of comparisons. The details of those experiments are described in Appendix A.

The carcinogenic effect of ammonium-plutonium pentacarbonate in rats has been found to be no greater than that of less-aggregated plutonium citrate [53]. Plutonium nitrate given by intratracheal injection [54], which results in highly localized deposition in the lungs, was significantly less effective than inhaled plutonium nitrate [55], plutonium citrate, and ammonium-plutonium pentacarbonate. However, intratracheally administered ^{210}Po in hamsters [56] has been more carcinogenic than inhaled ^{210}Po in rats [57] (although the significance of this is difficult to assess because of the different animal species used). In another experiment in which Pu microspheres of varying number and specific activity were distributed throughout the vasculature of the lungs of hamsters, no specific activity particle or dose distribution was found to be more carcinogenic than another, but a high incidence of lung cancer was not observed in any of the experimental groups [58]. A recent analysis [59] shows that the risk of lung cancer in rats from insoluble PuO_2 is about double that from relatively soluble alpha-emitters. In this analysis, data from experiments with relatively soluble americium and plutonium compounds were pooled. However, the lung cancer risk per unit of absorbed dose from some soluble alpha-emitters, such as $^{241}Am(NO_3)_4$, appeared to be equivalent to or greater than that from PuO_2 [59].

These animal experiments indicate that the carcinogenic response of lung tissue to alpha irradiation is largely dependent on the total amount of radioactivity without regard to its distribution. The maximum difference between the cancer risk from more particulate and from less particulate sources appears to be a factor of about 2. On the basis of these lifespan experiments, mostly with rats, it is possible to estimate that the absolute risk of lung cancer to rats exposed to inhaled transuranic elements is about 0.1% per rad over the dose range studied [59]. At the present time there is no basis for direct extrapolation of this risk estimate to the human being.

Studies [60] extending over the entire lifespan of beagle dogs conducted by Battelle, Pacific Northwest Laboratories have shown that bronchiolo-alveolar cancer is the principal type of lung tumor that develops in dogs after inhalation of an aerosol containing insoluble $^{239}PuO_2$ particles. More recently this same type of cancer has also been found in dogs exposed to aerosols of insoluble clay particles tagged with ^{90}Sr, ^{144}Ce, and ^{91}Y. In these experiments [61-63], which were conducted at the Lovelace Inhalation Toxicology Research Institute, the beagle lung received a diffuse, low LET (linear energy transfer) radiation exposure, as compared to the localized, high LET exposure produced by the ^{239}Pu particles.

The likelihood of a hot particle effect such as that envisioned by Cochran and Tamplin can be directly assessed from the results of the Battelle beagle dog study. The study was designed to simulate the kind of exposure which occupational workers involved in processing Pu might encounter; namely, inhalation of aerosols of $^{239}PuO_2$ particles generated during processing or accidental combustion of the metal. A group of 40 dogs was exposed at a relatively early age to an aerosol containing insoluble $^{239}PuO_2$.

Lung cancer in the Battelle group may for the purposes of the present discussion be thought of as derived from two sources: 1) generalized alpha irradiation of the lungs from $^{239}PuO_2$ particles and 2) any hot particle effect of the type proposed by Cochran and Tamplin. The extent to which any such hot particle effect contributed to lung cancer mortality in the dogs can be judged by comparing the observed number of lung cancer deaths with the number expected on the basis of Cochran and Tamplin's risk factor of 1/2000 per hot particle. The results of the analysis, details of which are presented in Appendix A, indicate that if there is a hot particle effect the cancer risk per particle is lower by at least several orders of magnitude than Cochran and Tamplin estimated. The analysis also shows that all of the lung cancer deaths in the Battelle group are readily attributable to the absorbed lung dose from the alpha radiation. In other words, if there is a hot particle effect the beagle experience indicates that it is dwarfed by the effect of the generalized alpha irradiation the dogs experienced. The results are summarized below.

As previously discussed, Cochran and Tamplin have defined the hot particle in two different ways. They originally described a hot particle as one with an associated lung cancer death risk of 1/2000 per particle and a specific activity of 0.07 pCi or more per particle. For brevity, we shall refer to this as the Type 1 hot particle. Later Cochran and Tamplin redefined the particle as one having the same cancer risk (1/2000 per particle) but they required that it have nearly ten times the specific activity, namely 0.6 pCi or more, to produce that risk. We shall refer to this redefined particle as their Type 2 hot particle. In order to avoid ambiguities in the following discussion, cancer risks will be assessed for both types of hot particles, since it is not clear that Cochran and Tamplin have completely abandoned the Type 1 definition.

The average animal in the Battelle group that died of lung cancer is estimated to have had deposited in the pulmonary lung regions approximately 1.3 million Type 1 particles and 200,000 Type 2 particles. These numbers are calculated on the basis of the measured particle size distributions of the aerosols the dogs inhaled.

On the basis of Cochran and Tamplin's assumed risk constant of 1/2000 per hot particle, it follows that the average dog would be capable of developing 650 lethal lung cancers, if they were produced by the 1.3 million Type 1 particles, or 100 lethal lung cancers if they were produced by the 200,000 Type 2 particles. It is important to realize that the actual number of primary lung cancers in an animal is not directly observable, even at autopsy, because lung tumors frequently metastasize, producing multiple foci which cannot be distinguished from multiple primary tumors. Nevertheless, since primary tumors are expected to arise as rare independent events and therefore to be distributed in accordance with the Poisson distribution [64], the mean number of lung cancers can be indirectly inferred from the observed cancer death rate. Thus, a lung cancer death rate is a measure of the probability of dying of lung cancer in a specified time period. More precisely, it is the probability of dying from at least one lung cancer in that period.

Cochran and Tamplin do not appear to have specified over what time period their proposed risk constant of 1/2000 would be realized. For the purpose of testing their hot particle hypothesis the mean life span of the normal unirradiated beagle, about 11.5 years, may be considered ample time for that constant to be fully realized. Since the average animal in the Battelle group was 560 days of age at the time of inhalation of the aerosol, the mean life span would be reached roughly 3600 days postinhalation. By Life Table methods it can be calculated (as shown in Appendix A-II) that if the average animal in the Battelle group had lived for 11.5 years, it would have had 1.9 primary lung cancers. According to the Cochran and Tamplin hypothesis there should have been 650 or 100 death-causing lung cancers in such a dog depending on whether the cancers were produced by Type 1 or Type 2 hot particles, respectively.

Thus the beagle data indicate that if there were a hot particle effect and if that effect were responsible for all of the lung cancer deaths in the animals, the associated risk of a lung cancer would still only be one chance per 670,000 per Type 1 particle, or one chance per 100,000 per Type 2 particle. These risks must be compared with the risk of one chance per 2000 which Cochran and Tamplin have postulated for either a Type 1 or Type 2 particle.

It remains to be considered whether the observed lung cancer mortality in the Battelle group can be accounted for solely on the basis of the dose received from the generalized alpha radiation. The effective half-life of this radioactivity in their lungs averaged 960 days. For the animals that died of lung cancer between 0 and 3600 days postinhalation, the initial lung burdens averaged 1.07 μCi. The resultant total accumulated dose to the lungs at 3600 days postinhalation was 2575 rad. For chronic exposures of this type, Marinelli has shown that tumor response is expected to be a function of the average accumulated dose [65], namely 1841 rad in the present case. Hence, the lung cancer risk extending over the period 0-3600 days was 0.1% per rad (1.9/1841), or 0.01% per rem (if a quality factor of 10 is assumed for the alpha radiation from ^{239}Pu). This estimate agrees well with corresponding estimates for other species under exposure conditions in which hot particles would be absent [59]. Thus, lung cancer mortality in the Battelle group appears to be adequately accounted for by the conventional method of averaging the absorbed alpha dose over the entire lung. Therefore it is concluded that if there is a hot particle effect the lung cancer risk per particle has not only been greatly overestimated but, more importantly, such a risk is small by comparison with the lung cancer risk attributable to the generalized alpha radiation.

It could be contended that the Cochran-Tamplin risk constant of 1/2000 per hot particle still applies to human beings, even though that factor is too high by orders of magnitude to be consistent with the beagle dog experience. However, such a contention loses its force when it is realized that Cochran and Tamplin derived that constant on the basis of induction of tumors in the rat. Moreover, these were not lung tumors but skin tumors, and they were induced not by localized alpha sources of the insoluble $^{239}PuO_2$ type but by a diffuse alpha irradiation.

It could also be contended that the beagles had far fewer hot particles in their lungs than estimated. Although such a possibility cannot be rigorously excluded, the beagle experiment simulated in many ways the worst possible type of exposure, in that the dogs inhaled a polydispersed aerosol of $^{239}PuO_2$ particles immediately after the aerosol was generated. Thus, there was a maximum opportunity for relatively large particles, such as Type 2 particles, especially, to reach the deep lungs. In contrast, in occupational accidents a worker would generally tend to inhale aerosols depleted rather than enriched in hot particles.

Finally, it should be stressed that sound radiation protection practice requires that the limits of exposure specified in a standard be expressed in quantities which can be relatively easily measured. In the case of alpha emitters of the ^{239}Pu type, the amount of radioactivity, and in turn exposure dose, which a person might acquire can be assessed by determining excretion rates supplemented where possible with whole body scanning. On the other hand, there is no way of measuring the number of hot particles which a worker might have inhaled short of extirpation of relatively large amounts of lung tissue.

It is further concluded on the basis of the Battelle beagle study that the current method of measuring the generalized alpha radiation provides an adequate and practical method of estimating potential lung cancer hazard. Studies in progress involving lower levels of inhalation of ^{239}Pu in the beagle should help to settle the question of whether there is any appreciable residual lung cancer risk that cannot be accounted for by the generalized alpha radiation.

EXPERIENCE WITH HUMAN BEINGS

The predominant types of lung cancer observed in human beings are epidermoid carcinomas, small and large cell undifferentiated cancers, adenocarcinomas, and mixtures of these types. All of these generally occur in the hilar region of the lungs and are more frequent in smokers, persons exposed to chemical carcinogens, and uranium miners [66].

Cancers in human beings have only rarely originated, under any circumstances, in the bronchiolo-alveolar regions [67]. Therefore, an excess incidence of carcinomas in these tissues as a result of occupational exposure to carcinogens would probably have been readily detected. Data on the relative frequencies of different tumor types in uranium miners and Japanese atomic bomb survivors suggest that the radiosensitivity of the bronchial epithelium for cancer induction may be greater than that of the alveolar or bronchiolo-alveolar tissues.

In animals, it has been determined from experiments that the bronchiolo-alveolar epithelium is the most likely site of primary lung cancer following inhalation of plutonium, as well as the predominant site of naturally-occurring lung cancer. Since plutonium is not known to have caused lung cancer in human beings, we do not know where such cancers might originate. The bronchial epithelium is the predominant site of human lung cancers, while cancers of the bronchiolo-alveolar epithelium, the region of the lung expected to receive the majority of the alpha dose from inhaled plutonium, are rare [66-68]. Thus, the site of plutonium-induced cancers in the human being will depend upon the relative cancer susceptibilities of the bronchial epithelium and the bronchiolo-alveolar epithelium, as well as the magnitude of the radiation dose to these two regions. If in human beings the region of the bronchiolo-alveolar epithelium (where plutonium is retained) is much less sensitive than the bronchial epithelium (which may be subjected to possible radiation exposure only during the brief period when plutonium particles enter or leave the lungs), then human beings might be less sensitive to cancer induction by plutonium than are experimental animals.

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APPENDIX A

I. RELEVANT PHYSICAL AND BIOLOGICAL DATA

PARTICLES*

A number of characteristics of inhaled alpha-emitting particles influence their potential for producing deleterious health effects. These factors (such as real size, aerodynamic size, chemical form, specific activity, density, history of the material and solubility) may influence particle deposition, retention, translocation and ultimately the alpha dose to cells and organs.

The elemental contents of alpha-emitting aerosol particles that may be encountered under accident conditions vary greatly. For example, the elemental content depends upon where in the nuclear fuel cycle the aerosol is generated. At some stages in the cycle transuranic elements are handled in relatively pure forms; in other stages the mass of the materials may be dominated by uranium. Obviously, the elemental and isotopic contents will change as functions of the specific fuel cycle and the radiation history of the material, including elapsed time since discharge from the reactor.

The range of variations in the potential elemental and isotopic content of particles that might be released may be better understood by considering various stages in different fuel cycles.

1. An accident involving a uranium-fueled light water reactor shortly after fueling with fresh fuel would likely result in release of low specific activity particles consisting largely of uranium, with modest quantities of beta-gamma-emitting fission products and very small amounts of alpha-emitting transuranics.
2. An accident involving a uranium-fueled reactor after a period of extended operation would likely release particles of modest specific activity largely consisting of uranium and beta-gamma-emitting fission products with moderate amounts of alpha-emitting transuranics. The alpha specific activity might be on the order of a few mCi/g.
3. An accident during certain stages of fuel reprocessing could release material similar to that described above; at other stages it could yield relatively pure elements, including pure transuranics with specific activities related to the nuclide contents.
4. An accident involving uranium-plutonium fuel assemblies, either during their fabrication or during reactor operations, could yield particles that are largely uranium with significant quantities of plutonium and, after irradiation, other transuranics and fission products. The alpha specific activity could be on the order of a few mCi/g, perhaps approximately that of pure ^{239}Pu.
5. During reprocessing of the uranium-plutonium fuel elements, releases could be encountered at various stages that would yield particles approximating the fuel elements in radionuclide composition. At some stages of the reprocessing relatively pure elements with specific activities related to the radionuclide contents might be handled.

The foregoing descriptions indicate that accidents in most stages of nuclear fuel cycles will probably yield particles with specific activites no greater than that of ^{239}Pu, and in many cases lower.

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*Prepared for the Committee's use by R. O. McClellan and the staff of the Inhalation Toxicology Research Institute

The aerosol particles may vary greatly in chemical form, depending upon the nuclear fuel cycle stage from which they are released. The forms being handled in the nuclear fuel cycle vary from a nitrate solution to an oxalate to an oxide of the various elements. Aerosols released from these processes have not been extensively studied but are likely to be equally diverse. Conventional processes and accident situations may also involve heat, resulting in release of materials with varying thermal histories.

Aerosols usually consist of particles with a variety of physical and chemical properties. In particular, a whole spectrum of physical particle sizes is usually present in a given aerosol, even when all the particles have the same chemical composition. The important property, physical density, may differ among different-size particles of a given chemical form [1]. Hence, the density distribution with respect to particle size must be considered in characterizing an aerosol. Also, the specific activities of particles may be different for different sizes [2]. Due to lack of detailed information, however, it is usually assumed that all particles in a given actinide aerosol under consideration are composed of material of the same chemical form, specific activity and physical density.

If particles in an aerosol are spherical or nearly spherical in shape, their sizes can be conveniently described in terms of their respective diameters. However, for irregularly shaped particles, physical size is more difficult to describe satisfactorily. It is customary to refer to irregular particles in terms of the projected area diameter; that is, the diameter of a circle whose area is the same as the area of the particle as seen in two dimensions, as in an optical or electron microscope (Figure A.I-1).

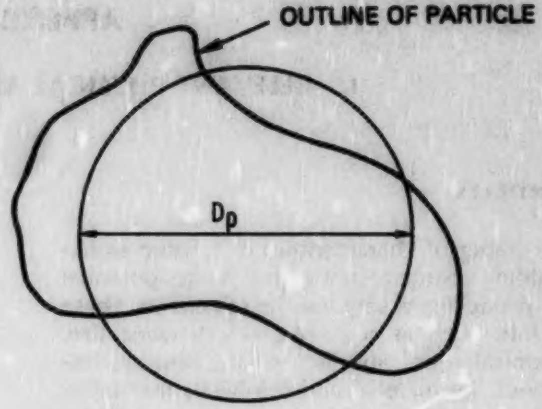

FIGURE A.I-1

Illustration of the Determination of the Projected Area Diameter, D_p, of an Irregular Particle

The size distribution, using either the diameter (D) of spherical particles or the projected area diameter, is most conveniently described as a mathematical function C(D) which is a probability density with

$$\int_0^\infty C(D)dD = 1 \qquad (1)$$

One such function which has been generally useful in describing aerosol particle size distribution is the log-normal function [3] given by:

$$C_1(D) = \frac{1}{D\sqrt{(2\pi)}\ln\sigma_g} \, e \, \frac{(\ln D - \ln CMD)^2}{2(\ln\sigma_g)^2} \qquad (2)$$

with ln the natural logarithm, D the particle diameter, CMD the median diameter of the distribution (count median diameter or geometric mean), and σ_g the geometric standard deviation of the distribution.

Other physical characteristics of the particles can be similarly described. For example, the surface area of the particle is important to a number of particle properties, including dissolution. An areal distribution with respect to diameter might be described as log-normal with an appropriate surface area median diameter (SAMD) and σ_g. If the volume or mass distribution of the particles is being considered with respect to diameter, these might be described with appropriate values for volume median diameter (VMD) or mass median diameter (MMD) and respective σ_g values. For actinides and other radioactive materials, the radioactivity distribution may be similarly described in terms of an appropriate activity median diameter (AMD).

Use of the log normal distribution function to describe aerosol property distributions with respect to size provides a number of useful mathematical transformations, including:

$$\ln \mathrm{VMD} = \ln \mathrm{CMD} + 3(\ln_e \sigma_g)^2 \qquad (3)$$

$$\ln \mathrm{SAM} = \ln \mathrm{CMD} + 2(\ln_e \sigma_g)^2 \qquad (4)$$

If the relationships among the volume, mass and/or specific activity of particles are known, Equation 3 can be used to calculate the MMD or AMD from the CMD and σ_g.

Aerodynamic properties of aerosol particles depend upon a variety of physical properties, including the sizes and shapes of the particles and their physical densities. When particles are inhaled, their aerodynamic properties combined with various aspects of respiratory mechanics determine their deposition in the respiratory tract, both in terms of fraction of those inhaled which are deposited and the location in the respiratory tract where they deposit.

Two important aerodynamic propeties of aerosol particles are the inertial properties (describable in terms of the settling speed in air under the influence of the earth's gravity under normal conditions) and the diffusional properties (describable in terms of the diffusion coefficient).

It has been customary to use an aerodynamic equivalent diameter (aerodynamic diameter, AD) to describe the inertial properties of aerosol particles. The aerodynamic equivalent diameter most generally used is defined as the diameter of a unit density sphere which has the same settling speed under gravity as the particle under consideration. Such an aerodynamic equivalent diameter is affected by all the factors (including shape, size and density) that determine the inertial properties of a particle. Under Stokes' Law for viscous settling conditions, the settling speed of a spherical particle is given by:

$$V_t = \frac{D_r 2C(D_r)g}{18\eta} \qquad (5)$$

and the aerodynamic equivalent diameter is given as

$$D_{aer1} = \frac{D_r \sqrt{\rho C(D_r)}}{\sqrt{C(D_{aer1})}} \qquad (6)$$

with D_r the geometric (or real) diameter of the sphere, ρ its density, $C(D_r)$ its slip correction, D_{aer1} the aerodynamic diameter and $C(D_{aer1})$ the slip correction associated with a unit density sphere of diameter D_{aer1}.

The slip correction, C, is a semiempirical factor that corrects the Stokes' Law of viscous resistance for the effect of "slip" between the air molecules when the aerosol particles are almost as small as or smaller than the free paths of the air molecules. The slip correction is approximated for spheres by

$$C(D_r) = 1 + A\left(\frac{2\lambda}{D_r}\right) \qquad (7)$$

with

$$A = \alpha + \beta \exp\left[-\partial\left(\frac{D_r}{2\lambda}\right)\right] \qquad (8)$$

with λ the mean free path as gas molecules, $\alpha \sim 1.26$, $\beta \sim 0.45$ and $\partial \sim 1.08$. At sea level the mean free path, λ, for air molecules is equal to about 0.0646 μm for air at 21°C.

Another definition for aerodynamic equivalent which has proved useful because of its simplified form is:

$$D_{aer2} = D_r \sqrt{\rho C(D_r)} \qquad (9)$$

D_{aer1} and D_{aer2} are nearly equal (within 0.1 µm), as approximately given by

$$D_{aer1} = \sqrt{\left[(D_{aer2})^2 + (A\lambda)^2\right]} - A\lambda \qquad (10)$$

where all dimensions are in micrometers, λ is the mean free path of air molecules and A is a constant equal to about 1.26 (from Equation 8).

The geometric diameter of spherical particles can also be calculated from the aerodynamic equivalent diameter as approximately given by:

$$D_r = \sqrt{\left[\frac{(D_{aer2})^2}{\rho} + (A\lambda)^2\right]} - A\lambda \qquad (11)$$

All properties of the geometric diameter described also apply to the aerodynamic diameter. For example, one can refer to the count median aerodynamic diameter (CMAD), the mass median aerodynamic diameter (MMAD) and radioactivity median aerodynamic diameter (AMAD).

The rate of solubility of small, relatively insoluble particles is affected by the physical property, surface-to-mass ratio. For a small particle, the surface area is high relative to the mass and this greater relative exposure to the solvent will enhance dissolution. This effect can be important in describing the dissolution of inhaled particles deposited in the lung.

Mercer [4] discussed the importance of particle size distribution in determining the solubility of inhaled aerosol particles of relatively insoluble forms. According to Mercer, film diffusion kinetics do not control the dissolution of sparingly soluble materials; rather, the dissolution rate for a single particle is given by:

$$\frac{dM}{dt} = -ks \qquad (12)$$

where M is the particle mass, s is the particle surface area, t is time and k is the dissolution rate constant of specific solubility which has units of mass or radioactivity dissolved per unit time per unit surface area of the particles. Equation 12 is equivalent to Equation 13:.

$$\frac{dF}{dt} = -\frac{k'}{D} \qquad (13)$$

where F is the mass fraction, D the particle diameter and k' a constant equal to $k\alpha_s/\rho\alpha_m$ with k the rate constant of specific solubility, α_s the particle surface shape factor, α_m the particle mass shape factor and ρ the particle density.

Unfortunately, dissolution rate constants for various chemical forms of familiar materials are not readily available at this time because chemists have customarily described solubility in terms of the equilibrium solubility product, which does not apply to nonequilibrium dissolution as described by Equation 12. However, dissolution rate constants have been measured under certain conditions [5]. Results reported by Raabe et al. [6] indicate significant differences related to the specific elements as well as differences between ^{238}Pu and ^{239}Pu (Table A.I-1) [7].

Aerosols usually consist of particles with widely varying sizes, such as those which might be described with log normal size distributions. Such particle dispersions are called polydisperse, to emphasize the various sizes and types of particles that may be present. When an aerosol consists of particles of only one size, shape and type, it is referred to as monodisperse. A practical definition of mono-

TABLE A.I-1.

172 Reload Fuel Assemblies
(in g/1000 MW[e])

Nuclides	BWR Uranium	1.15 SGR* Recycled Pu
^{234}U	7.57×10^4	4.64×10^4
^{235}U	8.40×10^5	5.93×10^5
^{236}U	2.10×10^4	1.26×10^4
^{238}U	3.14×10^7	3.10×10^7
^{238}Pu		2.03×10^4
^{239}Pu		2.46×10^5
^{240}Pu		1.60×10^5
^{241}Pu		8.98×10^4
^{242}Pu		6.92×10^4
Total	3.22×10^7	3.22×10^7

---

*Self generating recycle assumes blending old plutonium that has been recycled three times with new plutonium formed in uranium fuel rods.

disperse is that the coefficient of variation of the size distribution does not exceed 20%. For a log-normally distributed aerosol, this is about equivalent to a distribution with σ_g less than 1.2.

Aerosol dispersions also depend for their properties on the state of the medium gas. Such environmental conditions as relative humidity, temperature, barometric pressure and fluid flow conditions (wind velocity, for example) will affect the aerodynamic phenomena associated with aerosol particles.

Another property of a given aerosol dispersion that can be of great importance in affecting particle behavior is the state of electrostatic charge. In some cases, aerosols released in the nuclear industry might be expected to have a significant charge per particle that could be a major factor in determining their deposition, collection or coagulation.

The most basic dispersion properties of aerosols are those that relate to the particle concentration in air or other gaseous medium. The number of particles per unit volume of gas (#/cm^3) indicates the coagulation rate of the particles. The mass concentration (mg/m^3) and radioactivity concentration (pCi/ℓ) provide the quantitative information on which inhalation exposure levels may be calculated.

Our knowledge of the specific characteristics of aerosols encountered within containment systems for normal operations is limited and that of the characteristics of accidentally released aerosols is even more limited. Elder et al. [8] measured some parameters for aerosols collected from the process or glovebox ventilation ducts that make major contributions to overall activity concentrations incident on exhaust HEPA filters. They found a spectrum of aerosol sizes. A plutonium recovery plant yielded aerosols in which over 70% of the particles were under 1 μm AD; a fabricating plant produced aerosols in which over 50% of the total activity was associated with particles in the 1-5 μm AD range; and research and development facilities produced a broad spectrum of particle sizes, usually in the 1-2 μm AD range (Table A.I-2).

Raabe et al. [6] recently evaluated the aerosols present in a glovebox during a plutonium oxide and uranium oxide mixing operation and found the Activity Median Aerodynamic Diameter to be 1 to 3 μm with a σ_g less than 2 when the aerosol was drawn through an electrostatic discharger (Table A.I-3). Preliminary studies by Raabe et al. have indicated that the plutonium in these industrial aerosols is much more soluble than laboratory-produced $^{239}PuO_2$.

Mann and Kirschner [9] reported limited data obtained from a fire in a plutonium facility. They measured a Mass Median Diameter of 0.32 μm with a geometric standard deviation of 1.83 using an autoradiographic technique on particles collected 15, 25 or 50 feet from the fire. Kanapilly et al. [10] reported solubility data on a plutonium aerosol collected in another accident and reported that the plutonium was much more soluble than laboratory-produced $^{239}PuO_2$ aerosols.

TABLE A.I-2.

Plutonium Aerosol Size Characteristics [8]

Activity median aerodynamic diameter (AMAD)

At Location —,	— %	of — Observations	Fall in the Range — μm — μm
A	86	77	1.0-3.0
B	62	26	1.0-4.0
C	92	48	3.0-5.0
D	89	18	0.1-1.0
E	84	49	2.0-4.0

Geometric Standard Deviation (σg)

At Location —,	—%	of — Observations	Fall in this Range
A	86	77	1.5-3.0
B	81	26	1.5-3.5
C	92	48	1.5-2.5
D	67	18	1.5-4.0
E	71	49	1.5-3.0

TABLE A.I-3.

Data Summary for Samples from an Industrial Plutonium Glove Box [6]

Day-Run	Sample Time (min)	AMAD (μ m)	σ_g	Conc. (nCi/l)
		I. IMPACTOR SAMPLES		
2-2	3	1.70 ± 0.05 S.E.	1.62 ± 0.04 S.E.	25
3-2	3	2.26 ± 0.11	1.63 ± 0.05	85
3-3	3	1.80 ± 0.06	1.51 ± 0.04	44
3-4[a]	3	5.02 ± 0.89	3.20 ± 0.53	2
3-5[a]	3	3.80 ± 0.32	2.16 ± 0.14	1
		II. LAPS SAMPLES		
1-1	45	1.56 ± 0.03 S.E.	1.51 ± 0.02 S.E.	20
2-1	60	1.44 ± 0.07	1.54 ± 0.06	41
3-1	90	2.56 ± 0.11	1.70 ± 0.05	8

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[a] No ^{85}Kr discharger, sample data not used.

RESPIRATORY TRACT STRUCTURE AND FUNCTION*

Basic Anatomy

Many anatomical features of the respiratory tract influence deposition and retention of inhaled aerosols, including lung volume, alveolar surface area, and structure and spatial relationships of conducting airways and alveoli. The distribution of radiation doses and effects of the inhalation of radioactive aerosols depend on the characteristics of the aerosol-emitted radiation and upon the deposited particles' proximity to the cells at risk.

The respiratory tract may be considered as having three major regions: the nasopharyngeal, the tracheobronchial, and the pulmonary. The nasopharynx filters out large inhaled particles and is the region in which the relative humidity is increased and the temperature of the air is moderated. The trachea, bronchi, and bronchioles serve as conducting airways between the nasopharynx and alveoli, where gas exchange occurs. The conducting airways are lined with ciliated epithelium and coated with a thin sheet of mucus. In addition to conducting air to the regions of gas exchange, the airways increase the relative humidity of air and moderate its temperature. The surface of the airways serves as a mucociliary escalator, moving particles from the deep lung to the oral cavity so that they may be swallowed. The branching patterns and physical dimensions of the airways are critically important in determining deposition of particles in the lung. They can be best demonstrated by a plastic cast of the airways (Figure A.1-2).

An early model describing the physical dimensions of the airways was developed by Findeisen [11]. These early data (Table A.I-4) were based more upon air flow considerations than anatomical measurements. Landahl [12], Davies [13] and Weibel [14] followed Findeisen with improved anatomical models based upon symmetrical airway branching. Weibel's model is shown in Table A.I-5.

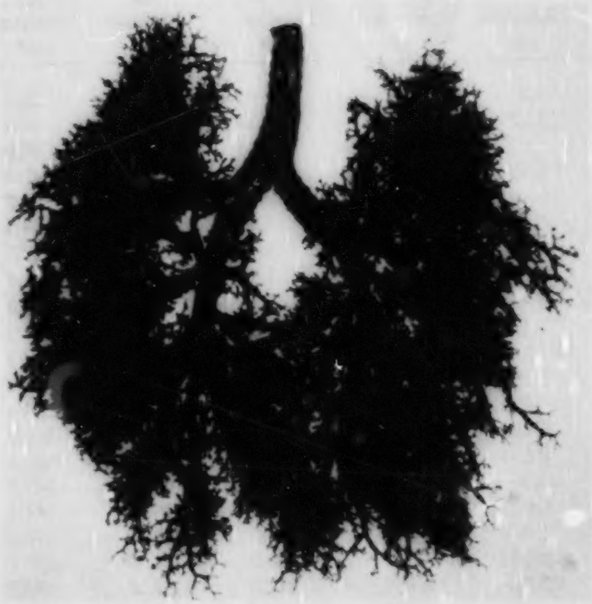

FIGURE A.I-2

Front View of Human Lung Cast Trimmed Down to the Level of Respiratory Bronchiole

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*Prepared for the Committee's use by R. O. McClellan and the staff of the Inhalation Toxicology Research Institute

TABLE A.I-4.

Model of the Human Bronchial Tree [11]

Region	Number	Diameter cm	Length cm	Total Cross-Section Area, cm^2
Trachea	1	1.3	11.0	1.3
Main Bronchi	2	0.75	6.5	1.1
First Order Bronchi	12	0.4	3.0	1.5
Second Order Bronchi	100	0.2	1.5	3.1
Third Order Bronchi	700	0.15	0.5	14
Terminal Bronchi	5.4×10^4	0.06	0.3	150
Respiratory Bronchioles	1.1×10^5	0.05	0.15	220
Alveolar Ducts	2.6×10^7	0.02	0.02	8200
Alveolar Sacs	5.2×10^7	0.03	0.03	(147,000)[a]

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[a] Total surface of the spherical alveolar sacs.

TABLE A.I-5.

Weibel's Model of Regular Dichotomy [14] (Average Adult Lung with Volume of 4500 mℓ at about 3/4 Maximal Inflation)

Region	Generation z	Number per Generation n(z)	Diameter cm	Length cm	Total Cross Section cm^2	Total Volume cm^3	Accumul. Volume cm^3
Trachea	0	1	1.8	12.0	2.54	30.50	30.5
Main Bronchus	1	2	1.22	4.76	2.33	11.25	41.8
Lobar Bronchus	2	4	0.83	1.90	2.13	3.97	45.8
	3	8	0.56	0.76	2.00	1.52	47.2
Segmental Bronchus	4	16	0.45	1.27	2.48	3.46	50.7
	5	32	0.35	1.07	3.11	3.30	54.0
	6	64	0.28	0.90	3.96	3.53	57.5
Bronchi with	7	128	0.23	0.76	5.10	3.85	61.4
cartilage in wall	8	256	0.186	0.54	6.95	4.45	65.8
	9	512	0.154	0.54	9.56	5.17	71.0
	10	1,024	0.130	0.46	13.4	6.21	77.2
Terminal Bronchus	11	2,048	0.109	0.39	19.6	7.56	84.8
	12	4,096	0.095	0.33	28.8	9.82	94.6
Bronchioles with	13	8,192	0.082	0.27	44.5	12.45	106.0
muscle in wall	14	16,384	0.074	0.23	69.4	16.40	123.4
	15	32,768	0.066	0.20	113.0	21.70	145.1
Terminal Bronchiole	16	65,536	0.060	0.165	180.0	29.70	174.8
Resp. Bronchiole	17	131,072	0.054	0.141	300.0	41.80	216.6
Resp. Bronchiole	18	262,144	0.050	0.117	534.0	61.10	277.7
Resp. Bronchiole	19	524,288	0.047	0.099	944.0	93.20	370.9
Alveolar Duct	20	1,048,576	0.045	0.083	1,600.0	139.50	510.4
Alveolar Duct	21	2,097,152	0.043	0.070	3,220.0	224.30	734.7
Alveolar Duct	22	4,194,304	0.041	0.059	5,880.0	350.00	1,084.7
Alveolar Sac	23	8,388,608	0.041	0.050[a]	11,800.0	591.00	1,675.0
Alveoli		300,000,000	0.028	0.023			

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[a] Adjusted for complete generation.

The acinus is the basic functional unit of the mammalian lung and the primary location of gas exchange between the environment and blood. Anatomically, the acini consist of the structures distal to and including the first-order respiratory bronchiole, which is the first bronchiole with alveoli. The acini, of which there are about 200,000 in the adult human, include 3 or 4 orders of respiratory bronchioles, several orders of alveolar ducts and alveolar sacs, hundreds of alveoli and associated blood vessels, lymphatic tissues, supportive tissues and nerve enervation. Air-containing portions of the acinus are depicted in Figure A.I-3 from reference to published drawings [15-17] and from examination of replica casts of the human lung [18]. Quantitative anatomical information for these structures includes estimates of airway tube numbers, diameters, lengths, alveolar numbers and diameters, surface areas and mean thicknesses for the air-blood barrier [13,14,19-23]. Variations in the acini from individual to individual and from species to species during growth, during breathing, and in healthy and unhealthy states have been described quantitatively by a number of authors [24-30].

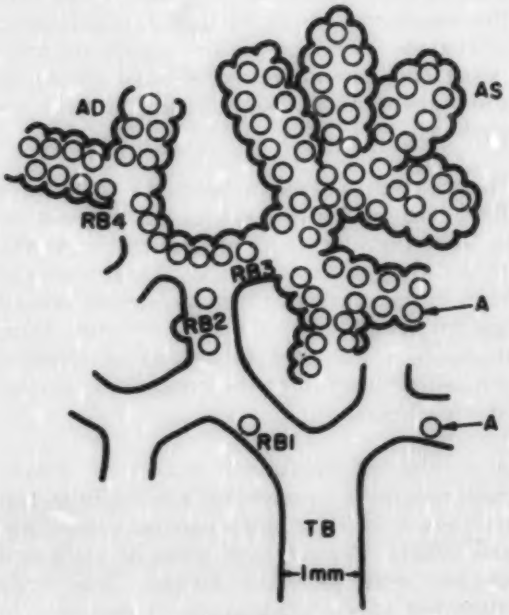

FIGURE A.I-3

Air-Containing Portions of the Acinus

Respiratory bronchioles are tubular structures with diameters of about 0.5 mm and lengths of about 1.0 mm in the adult man [15]. Bronchioles are lined with low cuboidal epithelium and at times with ciliated epithelium. Their walls contain collagen, smooth muscle, and elastic fibers, but no cartilage, which makes them quite distensible. One or more alveoli open to their lumens along one side while the other side is relatively smooth and in contact with branches of the pulmonary artery. In man, the number of alveoli opening into the lumen increases with each subsequent divison [15-17,20,31,32].

The alveolar ducts and sacs are thin-walled tubes, literally covered with alveoli on all sides. In adults their diameters are about 0.5 mm and lengths are about 0.7 mm [15]. Alveolar sacs, which are clusters of two or more alveoli terminating in one or more alveolus, branch from alveolar ducts and are essentially closed-end versions of ducts. The total number of alveolar ducts and sacs in man is estimated to be about 10-25 million [13,14,33,34].

Alveoli are thin-walled, polyhedral pouches with one side open to either a respiratory bronchiole, alveolar duct or alveolar sac. Thin, squamous pulmonary epithelial cells form most of the continuous inner lining of the alveolus. More rounded septal cells are also located within the walls and free motile phagocytic cells often lie in contact with the inner surface of the alveolus. A dense capillary vascular plexus covers the alveolus [31,35]. In man, the number of alveoli increases rapidly after birth until about 8 years of age [24,30], when approximately 300 million are present. The value of 300 million alveoli in the adult man is consistently reported, although recent estimates have ranged from 100 million [22] to over 500 million [13,36].

The alveolus of the adult human, though not strictly spherical, has an equivalent diameter of about 150-300 μm [13,14,21,22,24,37].

The values of 250-350 μm given by Weibel [14] are probably the most realistic. Alveolar dimensions vary with degree of lung inflation [38-40] and with their vertical positions within the thorax [41].

The total surface area of the alveoli in the adult man was reported by Von Hayek [37] as 35 m^2 during expiration and 100 m^2 during deep inspiration. Weibel [14] reported 70-80 m^2 at about 3/4 total lung capacity. The alveolar surface areas for several mammals are given by Tenney and Remmers [42].

The thickness of the air-blood barrier is variable, even for an individual alveolus. Weibel [43] summarized values for man from the work of Meessen [44] as follows: endothelium, 0.02-0.4 μm; basement membrane, 0.11-0.16 μm; alveolar epithelium, 0.04-0.065 μm; and total thickness, 0.36-2.5 μm. Tissue thickness between adjacent alveoli is determined by thicknesses of the alveolar wall, basement membrane, interstitium and any interposed capillaries. Weibel estimated that the capillary diameter is 8 μm and that 90 to 95% of the alveolar surface is covered by capillaries. Based on these data the mean tissue thickness between adjacent alveoli is about 9 μm. However, Weibel may be overestimating the abundance of the alveolar capillary network.

Lung Cytology

In addition to its major role as an organ for external gas exchange, the lung also performs numerous nonrespiratory functions [45]. A variety of cell types and systems are required to perform these diverse physiologic functions. One author [46] has listed well over 40 cell types as identified by ultrastructure, not including the circulating corpuscular elements of blood. Although some of the cell types are unique to the lung, many are present elsewhere within the organism. These include 17 types of epithelium, 9 types of unspecified connective tissue, 2 types of bone and cartilage, 7 types of cells related to blood vessels, 2 distinctive types of muscle cells, and 5 types associated with the pleural or nervous tissue elements. The cells of greatest interest are those that are unique to the respiratory tract, such as ciliated bronchial epithelium, nonciliated bronchiolar epithelium (Clara cells), squamous alveolar (type I) pneumocytes, great alveolar (type II) pneumocytes, and alveolar macrophages. In addition, three other cell types are of special interest: endothelial cells and interstitial cells (fibroblasts or fibrocytes), which comprise the greatest percentage of total cells present; and lining cells of the trachea and bronchi, which comprise only a small portion of the mass of the total respiratory tract. These latter three cell types are extremely susceptible to various types of injury.

Ciliated Tracheobronchial Epithelial Cells

The ciliated tracheobronchial epithelial cells are the predominant cells in the trachea, bronchi and bronchioles down to 1 mm in diameter, where they outnumber goblet cells 5 to 1. In the smaller airways they become more cuboidal and smaller and decrease in relative number. As the terminal bronchiole diminishes in diameter and terminates into the respiratory bronchiole, the cilia-bearing cells gradually disappear. These cells are polygonal and extend from the basal lamina to the lumen. About 500 cilia are present on each cell.

The ciliated epithelium functions to move a fluid film, and thus particles that deposit on it, from the lung to the nasopharynx [47-49]. Direct observations have shown that transport rates in the trachea or large bronchi in several species range from 1 to 3.5 cm/min. Thus, mucociliary transport is capable of cleaning inhaled particles from the conducting airways in a few hours.

A number of cytokinetic studies of airways have revealed a turnover time in the bronchial epithelium of 7 to 28 days in both mice and rats [50,51]. The turnover times of the bronchioles were generally longer. One study identified specific cell types in the bronchi and determined that the ciliated cell in the rat has a turnover time of about 130 days [53].

Nonciliated Bronchiolar Cells (Clara Cells)

Nonciliated bronchiolar cells are present only in small bronchioles and usually can be identified with light microscopy by their bulging into the bronchiolar lumen, by the absence of cilia, and by the presence of apical cytoplasmic granules identified as peroxisomes [53,54]. The ultrastructural characteristics [53] reveal the presence of plasma membranes that form complex interdigitations, including desmosomes, with adjacent epithelial cells. The general cytoplasmic features correspond to those of most secretory cells.

The cytochemistry of Clara cells [53-56] shows that lipids are present in cellular organelles in the form of bound lipids and probably as phospholipids. These, in turn, are firmly bound to a nonlipid component, probably protein in nature. Enzyme histochemical studies have shown high activities of oxidative enzymes [55-57] and the presence of acid phosphatase, alkaline phosphatase, and nonspecific esterase [56].

The function of the Clara cells is not known, although ultrastructural and cytochemical evidence indicates that they are metabolically active, probably secretory and have characteristics like merocrine-type secretory cells [53]. It has been suggested [58] and later supported [55] that Clara cells produce pulmonary surfactant. However, there is also a considerable body of evidence which supports the premise that pulmonary surfactant is largely a product of alveolar type II cells. Recently it has been proposed that Clara cells are the source of the hypophase (base layer) components of the alveolar lining layer, as opposed to the surface film (superficial layer) containing the surface-active phospholipids [53]. Another suggestion is that Clara cells supply surfactant for bronchioles [59].

Type I Pulmonary Epithelial Cells (Squamous Alveolar, Membranous Pneumocyte)

The surface of the pulmonary alveoli is largely covered by the continuous exceedingly attenuated (0.1-0.2 μm) cytoplasm of the squamous epithelium, which has nuclei resembling those of capillary endothelium. This cell is located on the epithelial side of the basement membrane and, together with the type II cells, completely lines the alveolus. The junction between the type I and type II cell is "tight", forming a zonulae occludens. The surface area of the type I cell has been calculated as 2290 μm^2 and that of type II as 63 μm^2. Thus, even though the ratio of type I to type II cells in the alveolus is 40:60, the type I cell makes up most of the barrier of the blood/gas pathway [60].

The cytoplasm of type I cells is barely visible with light microscopy and is equally unimpressive with electron microscopy because of its sparseness and paucity of organelles [61]. Except for pinocytotic vesicles, the cytoplasmic extensions are practically devoid of organelles except those concentrated in the perinuclear cytoplasm.

The squamous alveolar cells function as a pathway for gas exchange. Although they are relatively inactive metabolically, as shown by cytochemistry and electron microscopy, much activity must be involved in maintaining the membranes of such a large cell. Because they are in close contact with the environment, the squamous alveolar cells serve as the major epithelial barrier. Transport across the squamous epithelial cell is presumably by the pinocytotic vesicles [62]. Squamous alveolar cells have also been credited with phagocytic abilities under certain circumstances, both for substances from the blood [63] and from the alveolar lumen [64].

Type II Pulmonary Epithelial Cells (Great Alveolar, Granular Pneumocyte)

With the light microscope type II pulmonary epithelial cells are cuboidal. They are usually located in corners of the alveoli. The nucleus is spherical and the cytoplasm abundant with vacuoles. Great alveolar cells from a number of species have basically similar ultrastructure [65-67]. The cytoplasm has a loosely ordered granular endoplasmic reticulum, an extensive Golgi apparatus, numerous multivesicular bodies and many large osmophilic multilamellated inclusions or cytosomes. Together with the type I cell they line the pulmonary alveolus, with "tight" junctions between the cells. The surface area of the alveolus covered by the type II cell is not large compared to that covered by the type I; 11,000 μm^2 versus 259,000 μm^2 [60]. The plasma membrane of the type II has characteristic microvilli.

The numerous cytochemical studies of type II cells [65,68-72] show that they are rich in oxidative enzymes, acid hydrolases and esterases and have peroxidase activity. This indicates that the glycolytic scheme and the pentose cycle are active pathways of carbohydrate metabolism.

Type II cells are strongly implicated as producers of pulmonary surfactant. The evidence is cytochemical [65,70,72], ultrastructural [59,73,74], autoradiographic [74-77], and functional [78,79]. The ultrastructural and cytochemical characteristics indicate that type II cells are very metabolically active and are also secretory. The formation of the multilamellated bodies from multivesicular bodies with their subsequent excretion into the lumen has been ultrastructurally determined. The multilamellated bodies and associated enzymes are found at the same time in embryonic development of the individual that surfactant is first detected. Radiolabeled precursors of dipalmityl lecithin are found to concentrate rapidly in the type II cells. Radiolabeled leucine is rapidly taken up in the endoplasmic reticulum and multilamellar bodies, indicating that intracellular protein transport occurs and that the lamellar bodies are storage granules.

Other functions of this cell have not been documented; however, the type II cell is frequently the proliferative cell in the repair of subtle diffuse injury to the squamous pulmonary epithelium, such as results from beryllium and oxygen toxicity [80-82]. The type II cells nave been classified as a renewing cell population by several investigators [83], with relatively long turnover times ranging from 20 to 84 days.

Alveolar Macrophages

Alveolar macrophages are the phagocytic cells of the lung and are found free in the alveoli. With light microscopy, alveolar macrophages in tissue sections are ovoid mononuclear cells, 7-10 μm in diameter. The nucleus is 5-6 μm in diameter and round, oval or kidney-shaped. Macrophages washed from the lungs look similar except they are larger (15-25 μm) and flatter and have more definitive cytologic detail.

Many authors have described the ultrastructure of the alveolar macrophage [84-90]. The most notable features are the numerous single membrane-bound vacuoles, which are either scattered through the cytoplasm or arranged about the centrosome. These vacuoles vary in size, shape, internal structure and electron density. While some have a homogeneous matrix, others are multivesiculated and still others are composed of concentric layers of osmophilic membranes. The cytoplasmic membrane characteristically has many broad irregular extensions or pseudopodia.

The cytochemistry has been well studied by a number of authors [65,71,91-94]. Alveolar macrophages exhibit a high respiratory activity and depend on oxidative metabolism for energy required in phagocytosis. The abundant lysosomes present contain acid deoxyribonuclease, acid phosphatase, acid ribonuclease, arylsulfatase, DPN hydrolase, β galactosidase, β glucuronidase, β-N-acetylglucosaminidase, cathepsin D, lipase and lysozyme.

The origin of alveolar macrophages has been the subject of several recent reviews [93,95,96]. The relationship of the type II alveolar cell and the alveolar macrophage has not been definitively determined. Recent work using radiation chimeras and chromosome or enzyme markers for determining the origin of pulmonary washout cells shows that a majority of cells come from the bone marrow [96-99]. A four-compartment scheme has been proposed for the origin and maturation of alveolar macrophages based on evidence derived by following blood leukocyte counts, number of macrophages in lung washings and the tritiated thymidine labeling of alveolar cells after whole-body irradiation [100,101]. The postulate is that a stem cell in the bone marrow produces a cell which travels by the blood stream to the lung interstitium. Here the cell divides, matures and then migrates to the alveoli as a functional alveolar macrophage. Based on the radiographic indices, it was estimated that the time from cell division in the bone marrow to arrival in the lung interstitium is about 10 days, with approximately 10 more days required for maturation in the interstitium and arrival in the alveolus.

Cell renewal in the lung has been studied with tritiated thymidine labeling techniques [102,103] and with colchicine-stimulated mitotic indices. Both techniques show two populations in the alveolar wall, one with a turnover time of 7 days and another of 28-35 days. The cells in these populations have not been definitively identified but the 7-day cycle probably is representative of alveolar macrophages. The 35-day cycle may represent the type II or, less likely, the type I pulmonary epithelial cells.

The major function of alveolar macrophages is the ingestion of inhaled particulate material [104]. Infectious particles are usually killed by the macrophages, except in some chronic bacterial and fungal infections, such as tuberculosis, and in some viral diseases where the virus actually replicates in the macrophage [105-107].

The ability of pulmonary macrophages to ingest inanimate particulates has been documented many times [48,84,85,108-111]. Direct semiquantitative relationships between the number of phagocytes washed from lungs and the amount of dust cleared from the lungs have been demonstrated.

Endothelial Cells

The endothelial cells form a continuous cytoplasmic tube lining the pulmonary vasculature. They have thin cytoplasmic extensions which originate from a thicker central portion where the nucleus is located and are unimpressive with light microscopy. With electron microscopy [60,61,112] the endothelium shows few organelles except for numerous pinocytotic vesicles. At the intercellular junctions the two adjoining cells become closely approximated or may interdigitate and overlap. In either case, a narrow cleft exists which allows the passage of small protein molecules from the plasma to the extracellular space [112,113]. A small amount of protein is transferred via pinocytotic vesicles. The endothelium of the alveolar septa is separated from the epithelium by an interstitial space of variable thickness.

Cytochemical studies [57,114,115] show that the oxidative enzymes of the pulmonary endothelial cells are similar to those in the type I cells and are much less than those in other pulmonary cells.

The pulmonary capillary endothelium functions to exchange gases and volatile metabolites between the blood and air. However, these cells may also interact with the blood that perfuses them and perform functions with significant implications. For example, a lipolytic system in or on the surface of endothelial cells may be the source of a circulating lipoprotein lipase [116] and fibrinolysin is activated by substances in or on the vascular endothelium [117]. Five-hydroxytryptamine is removed from circulation by pulmonary endothelial cells, as indicated by autoradiographic studies [118].

The pulmonary endothelial cells have been classified as stem-cell, renewing cell populations [83]. The turnover time has not been determined but must be long, a matter of years [119].

Pulmonary Fibroblast

The fibroblast is a cell of mesenchymal origin which is responsible for production of intercellular substances of connective tissues. These are relatively undifferentiated cells and it is probable that the fibroblasts found in the lung are similar to those elsewhere in the body. The young fibroblast, when viewed with the light microscope, has abundant cytoplasm surrounding the nucleus and less cytoplasm in the attenuated processes which extend from each end, giving the cell a spindle-shaped appearance. The nucleus of the active fibroblast generally has a prominent nucleolus and is somewhat elongated and oval-shaped. Older fibroblasts or fibrocytes tend to have little or indistinct cytoplasm; often all that can be seen is a pale, ovoid nucleus with a little chromatin encased in the surrounding connective tissue.

Ultrastructurally, the cytoplasm of active fibroblasts is rich in rough-surfaced endoplasmic reticulum and free ribosomes. Mitochondria and lysosomes are also common. The prominence of ergastoplasm is clear evidence for the secretory function of this cell and the cisternae of the endoplasmic reticulum are probably the sites of formation of the secretory precursors. There is also a well-developed Golgi apparatus. The secretory products are extra-cellular and represented by collagen and intracellular ground substances. Pinocytotic vesicles indicate active exchanges of materials between this cell and its environment [120].

In cytochemical observations of fibroblasts, Thompson noted the presence of chondroitin sulfates and hyaluronic acid, both of which are generally believed to be synthesized by the fibroblast. Fibroblasts also produce proteoglycans. Fibroblasts have been demonstrated to contain stainable enzymes, including alkaline phosphatase, beta-glucuronidase and leucine amino peptidase, but they have been shown to be negative for stainable acid phosphatase. Fibroblasts, when placed in a mixed tissue culture, tend to overgrow other cell types in the same culture, to synthesize collagen [121-123], and to extrude synthesized procollagen from the cell into the surrounding media [124].

Functionally, it is evident that the fibroblast is an active cell whose main function is the production of collagen and intercellular ground subtances. Extensive work has been performed on these functions, both *in vitro* and *in vivo* [121,122,124,125].

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APPENDIX A

II. FACTORS IN DOSE-RESPONSE RELATIONSHIPS

FATE OF INHALED PARTICLES*

A report of the Task Group on Lung Dynamics of the International Commission on Radiological Protection [1] describes models for the deposition and retention of particles in the human respiratory tract. In this report, the respiratory tract was viewed as consisting of three basic compartments: a) the nasopharynx, b) the tracheobronchial compartment, and c) the pulmonary compartment. The nasopharynx (NP) begins with the anterior nares and extends to the level of the larynx or epiglottis. The tracheobronchial (TB) compartment consists of the trachea and bronchial tree, including terminal bronchioles. The pulmonary compartment (P) consists of the more distal portions of the lung which are involved in functional gas exchange.

The model includes estimates of both the fractional deposition of inhaled particles with respect to aerodynamic size and the clearance of deposited particles from the various regions of the respiratory tract based on the particle properties. Deposition, defined as the process which accounts for the amount of inhaled or inspired material that remains after expiration, is accomplished by inertial impaction, gravitational settling and diffusion by Brownian movement. Inertial impaction is greatest for particles 5 μm and larger in diameter and occurs primarily in the NP and TB compartments. Gravitational settling, involving particles in the range of 0.5 to 5 μm, is of some significance in the NP and TB compartments but is even more significant in the P compartment. Diffusion, involving particles smaller than about 0.5 μm, is of great significance for deposition in the P compartment and, for very small particles, may be the process by which large quantities of radioactivity are deposited in the N-P compartment.

A comparison of the Task Group's deposition model for inhaled particles with recent experimental data from man has recently been completed by Mercer [2]. In Figure A.II-1 the total body deposition for two tidal volumes (solid curves), based on the predictions of the task group model, is compared with experimental data, with good agreement. Figure A.II-2, which compares deposition in the pulmonary compartment based on the task group model to the very limited experimental data available, suggests that the task group model may underestimate somewhat the fraction deposited in the pulmonary region from nasal breathing. However, the model provides a good working basis for estimation of the deposition of inhaled particles, including alpha-emitting radionuclides. Mercer's paper also presents similar figures for the nasal and tracheobronchical regions.

The retention of inhaled particles in the respiratory tract was also addresssed by the Task Group on Lung Dynamics Report [1].

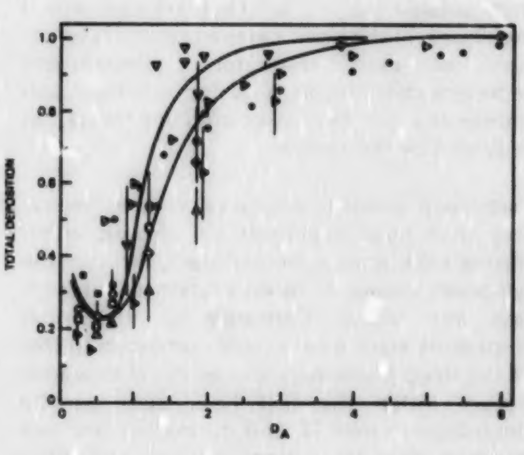

FIGURE A.II-1

Total Deposition During Nasal Breathing [2]

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*Prepared for the Committee's use by R. O. McClellan and the staff of the Inhalation Toxicology Research Institute

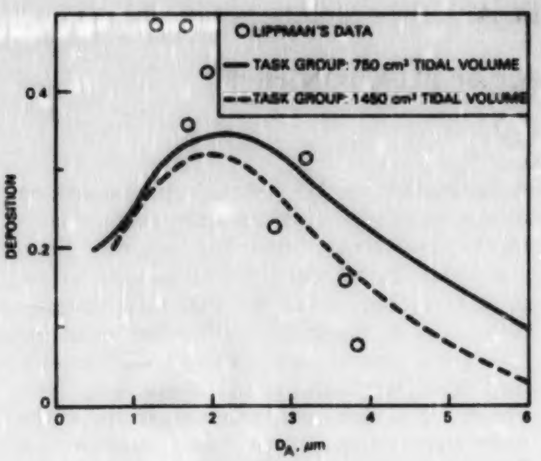

FIGURE A.II-2

Deposition in the Pulmonary Region During Nasal Breathing [2]

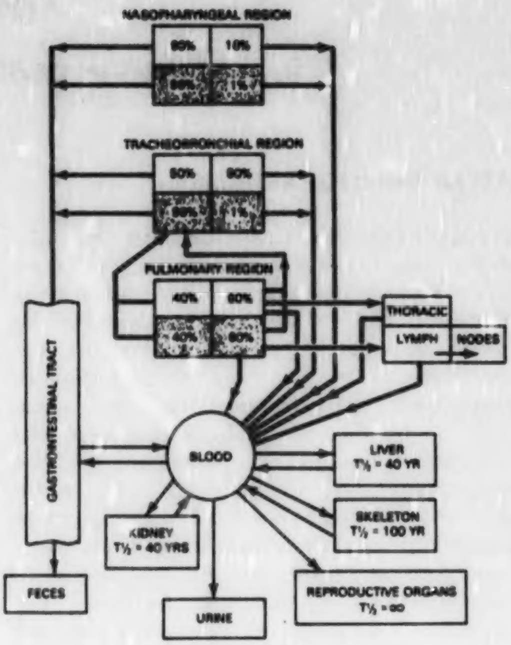

FIGURE A.II-3

Inhalation and Ingestion Model for Transuranic Elements in Man [3]

However, their model has been expanded by others to include the retention of inhaled material in the total body as well as in the lung. Figure A.II-3 illustrates the application of such a general model to transuranic elements in the environment (both inhalation and ingestion exposures) for man [3]. The cross-hatched areas represent deposition of very insoluble particles (i.e., $^{239}PuO_2$) as opposed to moderately soluble (i.e., $^{239}Pu[NO_3]_4$) aerosols which are shown in the open compartments. Percentages in each respiratory compartment represent those portions of deposited aerosols transferred by the associated pathways, as indicated by the arrows.

Particulate material deposited in the respiratory tract must eventually be cleared either through the gastrointestinal tract, through the lymphatic system, or by dissolution and absorption into blood. Clearance of the upper respiratory tract is very rapid compared to that of the deep pulmonary spaces. Nasal clearance occurs within the first hour after particle deposition in man [4] and during the first two hours in dogs [5]. Eating, sneezing and other mechanical functions speed nasal clearance, either to the environment or (by swallowing) to the gastrointestinal tract. Absorption of transuranic elements from the gastrointestinal tract is considered to be very small, ranging from 2×10^{-5} to 2×10^{-2} of the amount ingested for plutonium [6]. Radiation damage to the gastrointestinal tract itself from ingested alpha-emitters (even in enormous quantities) has not been demonstrated [7,8]. Thus the nasopharynx protects the lower respiratory tract regions from inhaled alpha-emitting radionuclides by diverting particles to clearance pathways, such as the gastrointestinal tract, that are not likely to be damaged.

Very similar considerations apply to material deposited in the tracheobronchial tree. Clearance times for these deposits, derived from studies [9] in mouth-breathing humans, are shown in Table A.II-1. Similar clearance rates have been reported for donkeys [10], which showed typical early clearance with a half-time of about 30 minutes followed by slower additional clearance during the remainder of the first day. Beagle dogs exposed to insoluble oxide or fused clay particles showed similar clearance of the tracheobronchial deposits during the first day following inhalation [11]. These cleared particles were subsequently swallowed and excreted in feces. For long-lived alpha-emitting radionuclides, radiation doses delivered to components of the respiratory tract or gastrointestinal tract during this short-term clearance are of doubtful significance, especially as related to long-term irradiation of deep pulmonary structures.

Particles deposited in the pulmonary region may be cleared via the lymphatic system, by mucociliary movement through the tracheobronchial tree, or by dissolution and absorption into blood. The relative importance of each pathway for a given aerosol depends upon many factors, such as the chemical form, particle size distribution, specific activity and elemental form. Mercer [12] suggested that dissolution of deposited particles in the deep lung region is the major pathway for clearance and that dissolution rates are directly proportional to the surface areas of the particles and their chemical compositions. Figure A.II-4 illustrates the potential influence of dissolution on the retention of inhaled transuranic elements in the lung. Figures A.II-5 through A.II-8 illustrate the variability in retention time in experimental animals and man for various forms and particle size distributions of some transuranic elements.

TABLE A.II-1

Average Bronchial Mucociliary Transit Times (90% Clearance) in Humans [9]

Subjects	Clearance Times (min)	No. Observations	S.D. (min)
Male (non-smokers)	494	14	130
Male (smokers)	439	15	156
Female (smokers)	324	6	55

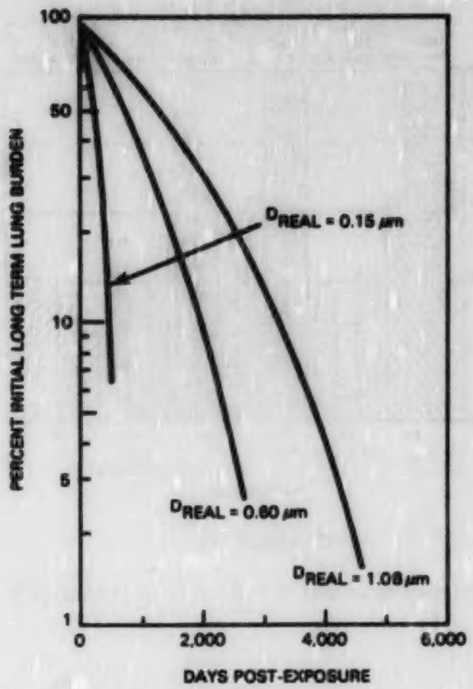

FIGURE A.II-4

Theoretical Lung Retention Curves for Monodisperse Plutonium Dioxide Aerosols of Various Sizes, Assuming Lung Retention is Solely Dependent Upon Particle Dissolution

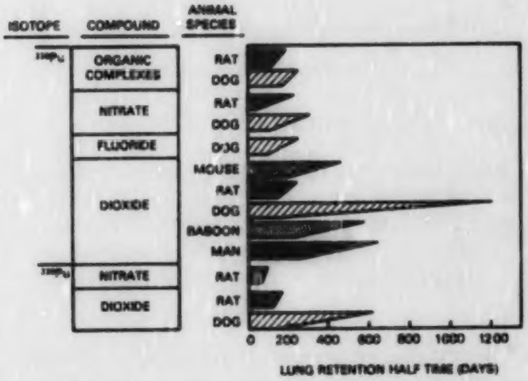

FIGURE A.II-5

Retention of Plutonium in Pulmonary Region of Lung [13]

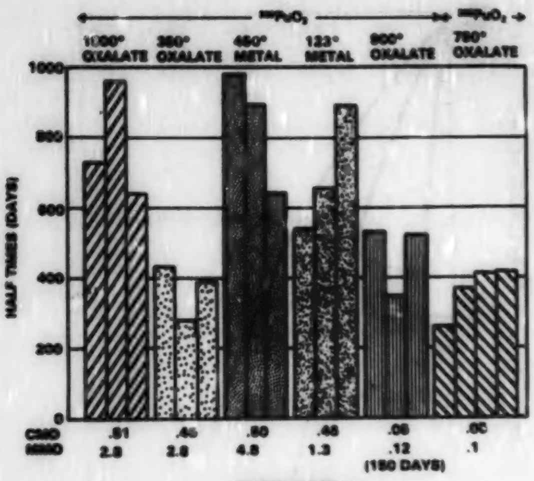

FIGURE A.II-6

Pulmonary Retention of Inhaled PuO_2 in Dogs [13]

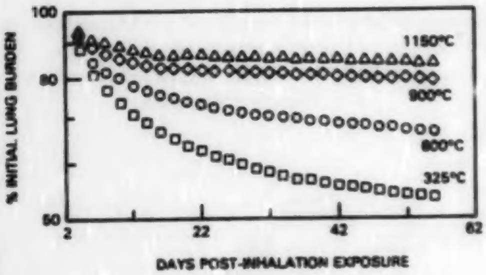

FIGURE A.II-7

Retention of ^{239}Pu in Dog Lung Expressed as a Precent of the Initial Lung Burden for Aerosols Produced by Heat Treatment of $^{239}PuCl_4$ at Four Different Temperatures (each set of data represents the mean of three values) [14]

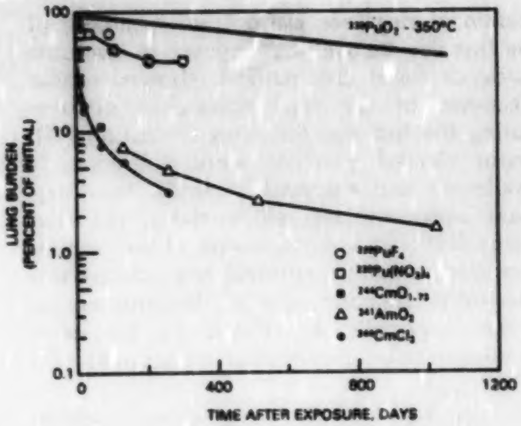

FIGURE A.II-8

Lung Retention of Inhaled Transuranic Elements in Beagle Dogs [13]

In the thorax, clearance of particles to lymph nodes occurs via lymphatic vessels that drain interstitial spaces. Particles must either penetrate the interstitium directly or gain access by transport in phagocytic cells. The Task Group on Lung Dynamics [1] recommended a half-time for lung clearance of 360 days for insoluble particles in humans. In ICRP Report 19 [15] a value of 500 days was adopted. One quarter of this total clearance is to lymph nodes with a half-time of about 2000 days. Other reports have incorporated a clearance half-time of about 7000 days for this process, or a fractional clearance rate of 0.0001 per day [11,16,17]. Even with the slower transfer of particles to lymph nodes, the concentration in these nodes was estimated to be more than 10 times greater than lung concentrations 6 years after inhalation of plutonium oxide aerosols. The absence of important biological consequences of lymph node deposits of alpha-emitting radionuclides will be discussed in later sections.

Clearance of the deep lung by way of the tracheobronchial tree and swallowing must also be a relatively slow and inefficient process. The effective lung clearance half-time has been reported as about 400 days in beagle dogs exposed to ^{90}Sr-^{90}Y-contaminated fused-clay aerosols [18]. Bair and Park [19] reported a total lung clearance half-time of more than 800 days in beagles for PuO_2 calcined at about 400°C. Although it is difficult to assess pulmonary clearance to the gastrointestinal tract from these studies alone, this clearance rate must be less than 0.2% of the lung burden per day and may be closer to 0.1% per day [11]. Differences reported for effective pulmonary clearance in the two experiments with beagle dogs probably relate to differences in particle solubility, although the effect of alpha radiation upon pulmonary clearance cannot be totally ruled out. Material that leaves lung tissue by absorption into blood distributes throughout other body tissues and is excreted. For absorbed plutonium and other actinide elements, ICRP Report 19 [15] suggests that 45% deposits in liver, 45% in skeleton and 10% goes into other tissues or is excreted. Effective half-times for plutonium in skeleton and liver were recommended as 100 years and 40 years, respectively.

PHYSICS OF ENERGY ABSORPTION*

Basic Particle Dosimetry

Whenever a charged particle traverses a medium, it leaves in its wake a number of ions, directly broken molecular bonds and, ultimately, free radicals (if the medium is aqueous). In turn, these free radicals also break molecular bonds, resulting in the largest portion of biologic effects attributed to such "indirect" causes.

The path of the particle and the distribution of the ions and resultant radicals are determined by the charge, mass, and velocity of the original particle. Electrons, being of relatively small mass and unity charge, produce some 6 ion pairs/μm of path (an energy loss of 210 eV/μm) when traveling with a velocity near that of light (say, for a particle energy of 1 MeV and higher). However, as the electron gradually loses energy, the path becomes very tortuous due to atomic and nuclear deflections. Also, the rate of energy loss increases because of the decreased velocity and increased time spent in the vicinity of atoms along the path. This loss increases to about 66 ion pairs/μm (2300 eV/μm) at an energy of 10 keV, which is near the end of its range. However, by this time, the electron has migrated many hundreds of micrometers from a co-linear projection of its original direction.

Thus, for a circular beam of electrons incident on a given medium, one visualizes a cylindrical volume filled with a reasonably uniform density of ions and/or free radicals. Consider a one-square-centimeter, 0.01 microampere beam of 5 MeV electrons incident on a water medium for one second, resulting in a delivery of 0.01 microcoulomb of charge. Thus, some 6×10^{10} electrons are delivered, depositing a total energy of 5×10^5 ergs. The range of these electrons is about 2.4 cm, leading to an irradiated volume of 2.4 mℓ or an irradiated mass of 2.4 g. Since the ions are distributed uniformly due to scattering, this corresponds to an energy deposition of 2×10^5 ergs/g or 2000 rad. The average energy loss is 5 MeV/2.4 cm or 5.6 ip/μm, which implies that the end of the range contributes little to the total loss.

One last figure of importance is that the total beam produces 9×10^{15} ion pairs, which leads to a spacing of about 0.06 μm between ion pairs. This in turn may be used to judge biologic effects relative to critical biologic structure. These considerations for electrons also hold for x-rays or gamma rays whose biologic actions are due to electrons produced by photon absorption.

Since alpha particles are some 7200 times heavier than electrons, their velocities are much lower for the same initial energy. Because of this, these heavy ions at nonrelativistic energies lose energy quite rapidly and produce a very dense column of ionization with very little deflection from their original path. Their range is also relatively short because of this high rate of loss along the path. In addition, due to statistical variations, there is about a 2% spread in the overall range of individual particles (straggling). A 5.3 MeV alpha particle with a range of 41 μm in water also has an average of of 129 keV/μm, or about 3500 ion pairs/μm. However, due to slowing down (with little deflection) the ion density increases by about a factor of 2 for 5 MeV particles at the end of their range. This is known as the Bragg effect and is much more predominant for alpha particles than for electrons.

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*Prepared for the Committee's use by E. C. Gregg

The alpha particle track is cylindrical, 90% of the ions remaining within a diameter of 0.01 µm. The remaining 10% are recoil electrons with sufficient energy to produce their own ionizations (delta rays). Such ions are present out to about 0.2 µm. This concept can be illustrated by considering a 5 MeV alpha particle beam of 6×10^{10} particles and an area of 1 cm^2, as for the electron beam discussed previously. Since the number of particles and the per particle energy are the same as for the electon beam, the same total energy of 5×10^5 ergs should be deposited. However, because the range is only 40 µm, a smaller volume is irradiated, resulting in a dose of 1.25×10^6 rad. To produce the same 2000 rad delivered by the electrons only 10^8 particles/cm^2 would be needed, which is a spacing of 1 µm, on the average, between incident particles. At the same time, the ion pairs are only about 3 Angstroms apart along the path of the particle.

These calculations of the dose in rad for alpha particles assume that the ionization is uniformly distributed throughout the volume, as with electrons and x-rays. That this restriction does not apply to alpha particles on the semimicroscopic basis is rather obvious, as discussed above. Furthermore, if the energy of one alpha particle were assumed to be deposited only in the volume of its path, this would result in 8×10^{-6} ergs deposited in 4×10^{-15} cm^3, or a local dose of 2×10^7 rad.

Radiobiologic Effects

The dosimetric considerations described above illustrate that the concept of dose in rad is not applicable to biologic effects where the volumes that are sensitive to radiation (i.e., the cell nuclei) are small and far apart in the milieu being radiated. It is well known that the nuclei of mammalian cells are at least a thousand times more sensitive to radiation than the cytoplasm [20]. Furthermore, heavily irradiating the cytoplasm seems to produce prompt cessation of all cellular functions, rather than just a loss of reproductive integrity, as found with irradiating nuclei. Regarding x-rays, a dose of 200 rad to a typical mammalian cell (e.g., Chinese hamster fibroblast) will prevent division (a genetic or reproductive death) half the time. Since typical masses of cell nuclei are 2×10^{-10} g, this corresponds to a delivery of 4×10^{-6} ergs to the nucleus, which in turn is 2.5×10^6 eV, or about 71,000 ion pairs. It is important to remember that this energy is distributed reasonably uniformly throughout the nuclear volume and is not all used to destroy critical molecules. Furthermore, the local molecular damage produced by forming one ion pair in the vicinity of a key molecule may be slight enough to allow subsequent repair or rejoining.

On the other hand, when an alpha particle penetrates the nucleus, the damage in the path of the particle is very high and repair is quite unlikely. Furthermore, there is no oxygen effect (enhanced production of free radicals in the presence of oxygen) as with x-rays. Thus, small doses of energy from alpha particles as averaged over the whole irradiated volume will produce the same effects as larger doses from electrons. A relative biologic effectiveness (RBE) ranging from 2 to 5 has been found for loss of reproductive integrity in mammalian cells by 5.3 MeV alpha particles, which implies that 50 rad due to an alpha particle averaged over the whole irradiated volume will cause the same damage as 100 to 250 rad of x-rays. Since any one 5 MeV alpha particle is depositing about 2×10^{-7} ergs/µm of path (which amounts to about 4000 rad when averaged over a cubical nucleus [7 µm x 7 µm x 7 µm]), even one particle will produce "overkill." This has been shown experimentally, in which only a 2 µm penetration of one alpha particle into a nucleus of approximately the size described above was necessary to kill the cell [20]. This data on "killing" or destruction of reproductive integrity by alpha particles can be explained on the basis that 50 rad corresponds to a spacing of 7 µm between alpha particles. This means that on the average a 7 µm-square nucleus will be hit by an alpha particle just a little over half the time.

Thus, instead of referring to dose in rad when dealing with alpha particles, we should more properly consider the probability of a cell nucleus being struck by such a particle.

Lung Model and Cells at Risk

To consider the lung, which is of immediate concern in the "hot particle" problem, assume the pieces of radioactive material are small enough (about 1 μm) to become trapped at any point in the lung and subsequently to radiate alpha particles in all directions. While the bronchial epithelium is probably more suspect than the alveoli as the tissue at risk, the following model of the epithelium in the alveoli is assumed to approximate the bronchial epithelium equally well.

An alpha particle that will traverse 40 μm of solid tissue will obviously travel much further in the less dense lung tissue, as the range varies inversely with the density (ρ). In addition, even though the total mass traversed along one path remains a constant, the number of cells within the increased volume determined by the range will be greater. The irradiated volume (v) varies inversely as the cube of the density while the total mass irradiated varies as ρv or $1/\rho^2$. Since the density of the actual cell does not vary, the number of cells at risk must vary as $1/\rho^2$.

Because the density of lung tissue changes during breathing, a number of different values are reported in the literature [21]. If the average lung (for men and women) weighs 1000 g, has a residual volume of 4.0 ℓ, and inspires about 1 ℓ under light exercise, a minimum density of 0.2 g/cm³ is produced at reasonable inspiration and a maximum density of 0.25 g/cm³ at expiration. Rather than average the density at this point, it will be more correct to average the cells at risk later in the calculations, even though the difference is small.

Microscopic examination of lung tissue shows that about 1/3 of the tissue traversed by an alpha particle located in an alveolus consists of epithelial cells; the rest of the tissue mass consists of blood, plasma and connective tissue. In spite of the fact that the cells are very irregular and widely dispersed, the volume of the cells and the projected cross-sectional area of the nuclei are of more concern. These are assumed to be 1500 μm^3 and 10 μm^2, respectively, for typical epithelial cells. The average cell, if forced into a cubical shape, is 11 μm on a side; if spherical, it is 14 μm in diameter. From the previous discussion,

alpha particle range (cm) = $R = 4 \times 10^{-3}/\rho$

lung volume - $V(\text{cm}^3) = 4500 + 500 \sin Wt$

angular respiratory frequency - W
$= 2\pi \times$ respiratory frequency

lung density (g/cm³) = ρ
$= 1/(4.5 + 0.5 \sin Wt)$

mass of tissue within $R = M(g) = 4\pi R^3\rho/3$

$$= \frac{8 \times 10^{-7}}{3\rho^2}$$

number of epithelial cells within $R = N$

$$= M/(3)\,(1500) \times 10^{-12} = \frac{60}{\rho^2}$$

To find the average number of cells at risk due to breathing we must average N:

$$\overline{N} = \frac{W}{2\pi} \int_0^{2\pi/W} N dt$$

$$N dt = \frac{60W}{2} \int_0^{2\pi/W} (4.5 + 0.5 \sin Wt)^2 \, dt$$

and evaluating,

$$\overline{N} = \frac{(1.01)60}{(\overline{\rho})^2}$$

where $\overline{\rho}$ is the linear average of the excursion due to breathing. Thus weighting the influence of breathing on the lung density only produces a 1% correction, which is negligible.

Using the originally assumed value for cell size,

$\overline{N} = 1240$ cells

$\overline{R} = 4 \times 10^3/\overline{\rho} = 182\ \mu m$

This yields an average volume of lung tissue per cell of 20,000 μm^3, or one cell in a box 27 μm on a side.

Probability Considerations

While the above calculations imply that six cells can occur sequentially along a 130 μm path, only three or four such cells can be penetrated, since these would completely absorb the energy of one alpha particle. Furthermore, since the total effective tissue path is still 40 μm, of which only 1/3 is cells, it follows that on the average only one cell will actually be in the path of an alpha particle, but the number hit can vary between zero and three. Since the nucleus is the critical target and it presents an area of 10 μm^2 to any incident particle, it would follow that the probability of not hitting a nucleus is 1 - 0.014 = 0.986. In a 180 um path there are roughly 7 (180/27 = 6.6) possible positions of nuclei, on the average. The probability of not hitting any nucleus in the total path is $(0.986)^7 = 0.9$; the probability of hitting one or more nuclei with at least one particle in the total path is 1 - 0.9 = 0.1.

One pCi of activity will emit 0.37 particles/sec or 3.2×10^4 particles/day. Considering the calculations above, we see that if Q is the activity in picocuries of any one source located in the alveoli, D days will be required on the average to sterilize all 1240 epithelial cells within the range of the alpha particles as given by $QD = 1240/(3.2 \times 10^4)\ (0.1) = 0.4$. This is plotted in Figure A.II-9. While a few cell nuclei in the critical volume are hit by more than one particle, delivery times longer than D days for a given Q simply mean that nearly all cells will be hit more than once (overkill region). Times shorter than D days obviously lead to underkill, as shown.

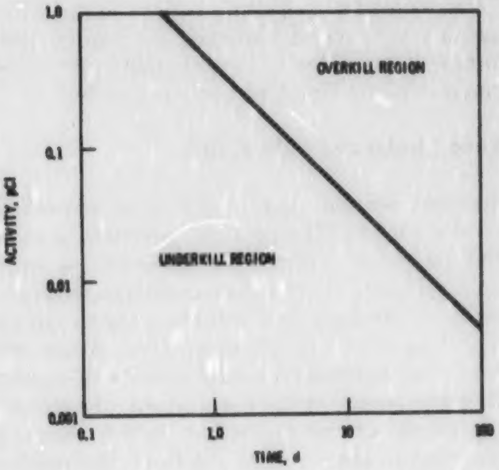

FIGURE A.II-9

Time Needed to Sterilize all Epithelial Cells

Since estimates of cell turnover in the lung range from 5 days to 80 days, even with cell turnover the effects of this type of radiation in terms of epithelial cell death will be the same for activities above about 0.005 pCi, as shown by the graph. There is no reason to suspect a precipitous change in the biologic effects at or near 0.07 pCi, as has been suggested on the basis of dose (in rad). In fact, this target treatment states that if turnover is neglected, two plutonium particles of a given activity located at different points in the lung will sterilize twice as many cells as one particle containing all the activity. While this effect has been found to hold approximately for tumor production in rat skin [22], extrapolation to lungs is not warranted because of turnover, particle migration, and dependence of initial distribution on particle size. Nevertheless, there is no apparent reason to support the concept of increased risk with particle activity above a certain level (∿0.005 pCi).

Irradiation of Rat Skin—Epithelial Cells

Albert et al. [23] found that irradiating the skin of rats with alpha particles produced tumors of the hair follicles only when the range was 0.35 mm or larger. Neither 0.12 mm penetration by alpha particles nor 0.16 mm penetration by protons produced any detectable tumors. Similarly, 0.2 MeV electrons did not produce tumors but 0.7 MeV electrons did [24]. Since the papilla which produces the cells for the medulla of the hair, the cortex, the cuticle and the internal root sheath is located at this depth, it is most suspect as the primary site of the induced tumors. (Even though many of these cells were in the telagen phase, they are capable of rapid regeneration.) Some tumors also apparently arose from the sebaceous gland located further up the hair shaft, but these also depended upon penetration of the radiation beyond about 0.35 mm.

It was also observed that no higher production of tumors was noted when the Bragg peak (x5 in dose in rad) was located at or near the papilla. The authors interpreted this to mean that the whole follicle must be irradiated to induce a tumor; it also seems logical to accept this as proof of the single particle "hit" hypothesis, which says that a single ionizing event is sufficient to cause a tumor.

Finally, and most interestingly, it was observed that no tumors originated in the heavily irradiated epithelial cells between the hair follicles. Data [25] on the epithelial cells in the basal layer of the skin indicate a population density in normal mouse skin of 1.4×10^6 cells/cm². This leads to a cell area of about 100 μm^2 or a cell size of about 10 μm on a side, which is close to that measured for most epithelial cells. Furthermore, the average nucleus is about 3 μm x 3 μm, which produces a cross-sectional area of about 10 μm^2. The alpha particle density used by Burns, Albert and Heimbach [26] was $10^8/cm^2$, or 1 particle/μm^2, for a calculated dose of 520 rad. This is a density of approximately 10 alpha particles per nucleus. If x is the average number of primary ionizations per target, then e^{-x} is the probability that no primary ionizations will occur in the target. It follows then for $x = 10$ that the number of nuclei not struck by an alpha particle is $N_S = (1.4 \times 10^6)e^{-10} = 60$ nuclei/cm². From Withers' data [25], 1300 rad of x-rays to the mouse skin will leave 60 survivors per cm², which leads to an RBE of 2.5 for the killing of epithelial cells by alpha particles if one measures the dose in rad as averaged over the whole irradiated volume. This is reasonably close to RBE values reported for reproductive death and other biologic effects produced by alpha particles [26].

In passing, it is interesting that Withers reported that 10 to 20 surviving epithelial cells were capable of preventing ulceration by proliferating to cover a 1 cm² area during a 10-day postirradiation period. A most important point in the alpha particle experiments by Albert et al. [23] is that all doses delivered to the rats killed about 10^6 epithelial cells each. Since 6 cm² were exposed per rat and 210 rats were irradiated, then about 10^9 cells were killed without producing one tumor. Thus the chance that one alpha particle passing through one epithelial cell will produce a tumor is less than one in 10^9, assuming that the probability of producing a tumor is proportional to the number of cells irradiated. This is equivalent to assuming tumors result from "near" misses which in turn produce appropriate genetic changes. Since a 5.3 MeV alpha particle in the lung, will, on the average, penetrate only one cell, the probability of its producing a tumor is less than 10^{-9} if the lung epithelial cells are like those in mouse skin.

Applying these findings to the hot particle concept, the probability of producing a tumor near such a particle is less than 1.2×10^{-6}. Furthermore, this probability is not dependent on the activity of the plutonium oxide particles, since for the ranges discussed no more than 1200 cells will be killed per particle. Only the number of particles is important. Also, if the density or proximity of similar cells is important in tumor formation, the above probability limit becomes even smaller since the epithelial cells in the skin are much closer together than in lung tissue.

Irradiation of Rat Skin—Hair Follicles

Tumor production in hair follicles has been considered as a model for tumor production in the lungs. Even though no structure in the lungs corresponds to the papilla in the skin, the epithelial cells in the alveoli appear to be similar in tumorigenicity to the potentially dividing cells in the papilla. This can be partially explained on the basis that the cells in the bulb of the hair follicle are an epidermal derivative [27].

The bulb of an average hair follicle in the rat is about 100 μm in diameter and 150 μm long, while the average cell in the papilla is quite similar in size to the epithelial cells described above [28]. Although not all of the bulb consists of potentially dividing cells, cells with measurable mitotic indices have been found in the root sheath extending 170 μm upward from the papilla. Thus the typical bulb can be approximated by a sphere 100 μm in diameter filled with about 1000 closely-packed, potentially dividing cells.

There are 2500 follicles involving a total of 2.5×10^6 cell per cm^2. This means that for an incident alpha particle dose of 10^8/cm^2 (520 rad), about 100 surviving cells should be distributed among 2500 follicles. Even if one surviving cell could regenerate a follicle, just as one epithelial cell can regenerate mouse skin [25], this would account for only a 4% follicle survival compared with an observed 85%. The implications, of course, are: 1) that many more cells are involved in a follicle than is assumed above, 2) that active cells migrate from unirradiated volumes to reform follicles, and/or 3) that wholly killed follicles appear "normal" due to the fact that most of the cells remain in a resting phase and are not challenged to divide. The latter is probably the most acceptable explanation.

More importantly, the alpha irradiation data indicate that one tumor is induced per 9000 abnormal hair follicles, or one tumor per 6×10^4 equally-irradiated hair follicles. Furthermore, for any of the doses used in these experiments, virtually all the potentially dividing cells in each follicle bulb are "killed" or rendered incapable of division. Thus, if we assume that 1000 closely packed cells or some fraction thereof must be rendered reproductively inert to form a nidus for a tumor, then tumor production should not depend on dose in these experiments. Since it obviously does depend on dose, the assumption of the necessity of a core of sterilized cells to produce a tumor is not valid [29].

It is much more reasonable to assume that the probability of producing a tumor is simply proportional to the total number of sterilized cells, since this will also be a measure of near misses that may create the appropriate genetic aberrations. The above example indicates that for 1000 cells per follicle, there should be a chance of creating 1 tumor per 6×10^7 sterilized cells. This leads to a probability of $(1/6) \times 10^{-7} = 1.6 \times 10^{-8}$ that a 5 MeV alpha particle in the lung will produce a tumor (assuming, of course, that the epithelial cells in the human lung are identical to those in the rat skin papilla). Thus, for the plutonium oxide particles that kill at most 1200 cells per particle, the probability of tumor induction is about 1 in 50,000 per particle, regardless of its activity.

While this value is much greater than that observed in either animals or man [30], most important is that this model says that uniformly distributed activity has a much greater tumorigenicity than that concentrated in a hot particle. The probability that a 0.1 pCi particle will induce a tumor in lungs containing cells like those in rat skin papilla increases from zero to 2×10^{-5} in 4 days, after which it remains constant. If that same activity is uniformly distributed in the lungs, then the chance steadily increases with time, becoming 2×10^{-4} at 4 days and 5×10^{-3} at 100 days. This illustrates an important difference between irradiation by hot particles and uniform distribution of radiation. In the former, for a fixed cell population, the chances of tumor production remain constant because all viable cells in the vicinity of each particle can be "killed" only once. On the other hand, with uniform distribution the chances of tumor production increase with time since cells are being continuously "killed". Cell turnover and possible particle migration may change the picture, but only slightly. However, if for no other reason than the fact that observable rat skin tumors appeared as early as 30 days after irradiation, it is most unlikely that there are cells of this type and sensitivity in the human and/or dog lungs in which the latent period for lung cancer is several years.

An exercise of interest is to determine the area of a possible single hit target for tumor production in the rat hair follicle. If A represents the target area and D the dose in particles/unit area, then AD is the average number of primary events occurring in the target. As before, the probability that a target will not be hit is e^{-AD}, producing for the number of survivors $N_S = N_O e^{-AD}$. From this we see $A = 1/D_{37}$, where D_{37} is the dose required to reduce N_S to 0.37 N_O.

In the data shown in Figure A.II-10 (from Heimbach et al. [31]) the percent of abnormal follicles is plotted against dose (in rad). Since the number of tumors is directly (and linearly) related to the number of abnormal follicles, one minus the percent of abnormal follicles is a measure of the number of survivors (i.e., those that do not get tumors). A plot of N_S versus dose (as shown in Figure A.II-10) shows that although the curve has only a slight shoulder (indicating an almost negligible extrapolation number but still implying possible repair), the straight line portion may still be used to determine A.

From the best straight line fit, D_{37} = 1000 rad, or an incident dose of about 2×10^{8} particles/cm^2. This leads to $A = 0.52\ \mu m^2$. The probability of one cell producing a tumor is finite only when this particular area is hit by one alpha particle. This might be an equivalent area just outside the whole nuclear membrane that will allow the cell to stay viable when hit, yet allow penetration by free radicals and/or delta rays to produce nonlethal genetic abberations.

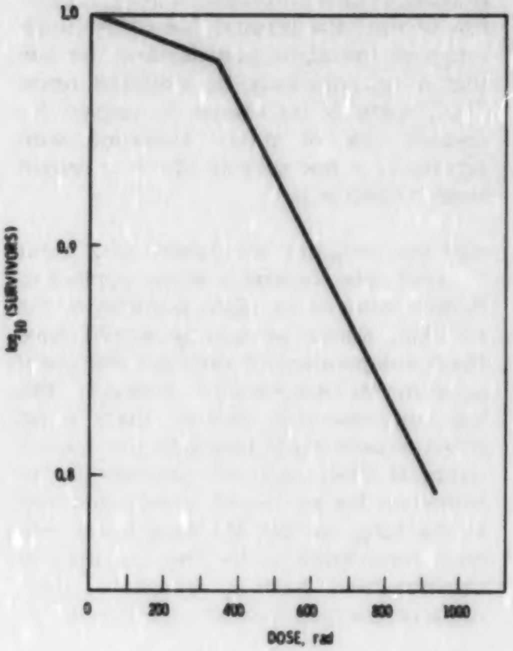

FIGURE A.II-10

Relationship Between Abnormal Hair Follicles and Radiation Dose (in rad) [31]

Conclusions

Fundamental dosimetric and radiobiologic considerations indicate that Cochran and Tamplin's "hot particle" concept and the Geesaman Hypothesis are invalid, for the following reasons:

1. It is incorrect to explain mechanisms of biologic effects of alpha particles in terms of dose in rad or rem, particularly when small, sensitive action sites are involved. However, it is appropriate to use dose in rad (or rem) for gross comparative purposes, provided the microscopic characteristics of the biologic media involved are reasonably similar.
2. Local ("point") concentrations of alpha-emitters can kill or affect only a fixed

number of cells and their progeny, regardless of the total activity, due to the finite range of the alpha particles and the fact that a cell can only be sterilized once. Thus, there is no reason to suspect increased risk of tumor induction with activity of a hot particle above a certain level ($\sim$0.005 pCi).

3. Had the proposed mechanism of a nidus of dead cells forming a tumor applied to tumors induced by alpha particles in the rat skin, tumor production would have been independent of dose for the doses used in the experiments; however, this was not observed. Further, there is no direct experimental evidence that such a nidus of dead cells will promote tumor formation for an already transformed cell in the lung. In fact, the lung tissue cells now considered to be the initiators of carcinogenesis have a reasonably short replacement time without such stimuli.

4. There is no evidence—histological or radiobiological—that any structures in the lung are similar to the cells in the bulb of the rat hair follicle. Thus, the probability of producing tumors in rat skin cannot be extrapolated to the human lung.

5. Models based on current radiobiological theory and experiments imply that the risk of carcinogenesis from a uniformly distributed alpha-emitter in lung tissue is higher than if the activity were concentrated in a few discrete point sources.

BIOLOGICAL EFFECTS

Cellular and Subcellular Effects*

The spectrum of effects on and in cells traversed by high LET radiations in general and alpha particles in particular has been studied in considerable detail. The general conclusion derived from these studies is that any particle with a LET of about 100 keV/μm has an exceedingly high probability of killing any cell whose nucleus it traverses.

Since almost all studies on cell effects are performed *in vitro* on cell suspensions or on single cell preparations, the effects are generally "direct" ones, in that any potential modification of cell injury influenced by the presence of adjacent normal unirradiated cells is likely to be absent or at least unphysiologic. An additional possible complication is that the mammalian cells studied *in vitro* are frequently characterized by a relatively rapid replication rate and morphologic uniformity. However, although the "nonphysiologic" nature of experimental culture media relative to a mammalian tissue milieu may influence the degree of response, in all likelihood it is not of major significance.

Some fifteen years ago Barendsen et al. [32] showed that cells irradiated by alpha particles, unlike low-LET x-rays, showed *in vitro* survival curves which could be described by simple exponentials of the form $S = e^{-kD}$, where S is fractional cell survival, D is the dose in rad and k is a proportionality constant describing the curve's slope. Assuming Poisson distributions, k can be shown to equal $1/D_O$ (i.e., one hit per target) and if D/D_O equals 1. (e^{-1}), D_O, is the 37% dose. Thus $S = e^{-D/D_O} = e^{-1} = 0.37$. The smaller the value for D_O, the steeper the slope and the more effective the radiation quality. For low LET radiations, such as those of x-rays, cell type often influences the precise value, but for mammalian cells D_O is generally 100 to 150 rad and 130 rad is a frequently quoted value describing the exponential portion of the survival curve [33].

Cells irradiated by alpha particles not only fail to manifest the low dose shoulder characteristic of x-ray exposures but also follow a steeper slope, with values of D_O ranging from 50 to 100 rad. A graphic comparison of cell survival following irradiation by x-rays and alpha particles (measured by cell cloning potential) is shown in Figure A.II-11 [32], in which the x-ray D_O is about 135 rad and that for alpha particles is 65 rad (^{210}Po). The authors calculated the "cell sensitive" area from the survival curve data as alphas per unit area passing through cells. Thus for their study, at 170 keV/μm (3.4 MeV α s), one α per μm^2 is equivalent to an average dose of 2720 rad. At a mean D_O of 65 rad, they calculated that the sensitive area was about 42 μm^2, and if circular had a 7.4 μm diameter. Since the human kidney cells used had optical diameters of 6 to 10 μm and (as will be shown below) the cytoplasm is not the likely "target", they concluded that

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*Prepared for the Committee's use by M. Goldman

> . . . the sensitive area is approximately equal to the area of the nucleus. This implies that whenever one α-particle penetrates the nucleus anywhere, the cell is sufficiently damaged to be prevented from developing into a clone. This does not imply that the sensitive volume is identical with the whole nucleus. It is quite possible that the sensitive structure is distributed inside the nucleus in such a way that the probability of an α-particle's passing through the nucleus without hitting this structure is very low.

> . . .the passage of one α-particle through the nucleus of a cell suffices to inhibit this cell irreversibly from developing into a clone, whereas cells not hit in the sensitive volume may be assumed to be damaged to such a small extent by α-particles passing through cytoplasm only that subsequent X-radiation will act on these cells as if they had not been irradiated at all. On the other hand, cells irradiated with X-radiation first, but not damaged sufficiently to be prevented from developing into a clone, will be expected to have the same sensitive area as cells not damaged at all, i.e., the cross sectional area of the nucleus. Indeed their sensitivity to α-radiation is not found to be increased or decreased by the preceding X-irradiation (curves 3 and 4, Figure A.II-12 [32]).

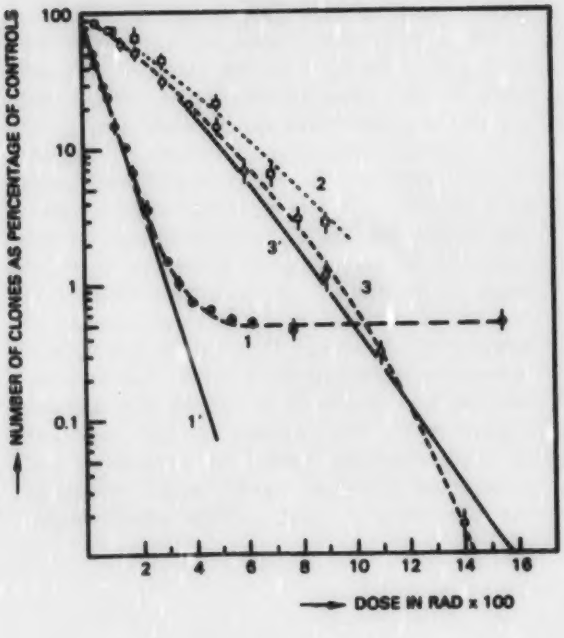


FIGURE A.II-11

Effects of α-, β-, and X-Radiation on Colony Formation [32]

Curve 1 obtained with α-radiation;
Curve 1' corrected for cells not adhering to the bottom of the dishes;
Curve 2 obtained with β-radiation, RBE 0.85;
Curve 3 obtained with X-radiation;
Curve 3' theoretical $n/n_O = e^{-D:135}\ (1 + D/135)$

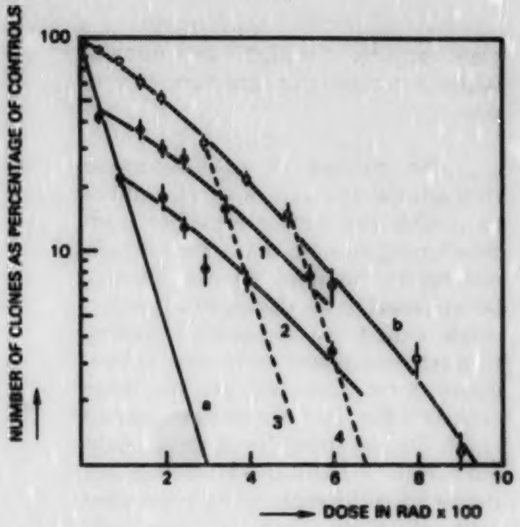


FIGURE A.II-12

Effects of Combined α- and X-Radiation [32]

a and b, effects of α- and X-radiation, respectively;
Curve 1, effects of 50 rad of α-radiation + 0, 100, 150, 200, 300 and 500 rad of X-radiation;
Curve 2, effects of 100-rad α-radiation + 0, 100, 150, 200, 300 and 500 rad of X-radiation;
Curve 3, effects of 300 rad of X-radiation + 0, 50 and 100 rad of α-radiation;
Curve 4, effects of 500 rad of X-radiation + 0, 50 and 100 rad of α-radiation

An experiment by Munro [29] vividly illustrates the relative insensitivity of the cell cytoplasm to alpha irradiation and shows that Barendsen's "sensitive area" is most likely the nucleus. Using a micro-manipulator, Munro was able to selectively irradiate single cultured Chinese hamster ovarian fibroblasts with ^{210}Po alpha particles with a ballistic precision of about 1 μm (Figure A.II-13). The flux density (α/m^2) was equivalent to about 2000 rad/μm^2 (Figure A.II-14). He showed that doses of 25,000 to 100,000 rad to the cytoplasm alone had little effect on subsequent cellular growth and proliferation, but that nuclear alpha irradiation was lethal (Figure A.II-15). Lethality seemed to correlate best with irradiation within ±1 μm of the cell nuclear membrane. The "partial" nuclear radiation doses used for the 1.4 μm "tails" at an exposure to 0.18 $\alpha/\mu m^2$ and 180 keV per tail over a 10 μm^2 area of nuclear surface of a 200 μm^3 volume resulted in a dose estimate of about 26 rad.

These studies suggest that if a small portion of the alpha particle energy is deposited at or near the nuclear membrane, cell lethality is quite likely. However, if the energy deposited within the nucleus is much below 100 keV (i.e., <1 μm) some cells may survive. Thus, "near" or partial cell nucleus radiation by alpha particles may have a lower relative biologic effectiveness and, although spatially different in terms of energy distribution, may resemble the effects of lower LET radiation traversals.

This low probability effect is inferred in the recent work of Hall [34], in which synchronized hamster cells manifested varying values of D_O as a function of the stage of the cell cycle at the time of irradiation. While the general response was qualitatively similar to that found following x-radiation (Figure A.II-16), with an "increase in radioresistance to a maximum in late S, followed by a sensitive period in late G_2 and M phases of the cycle," it is tempting to speculate that the spatial distribution of dose-to-nucleus may not be as significant as the total number of ionizations absorbed. There does not appear to be an especially sensitive subnuclear volume, but perhaps there is an ionization density dependence. The relation of LET and RBE for alpha particles found by Barendsen [35] is depicted in Figure A.II-17, which compares the unit dose to unit particle effectiveness.

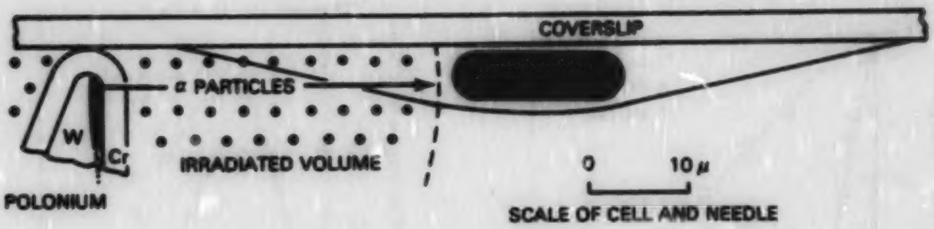

COVERSLIP
α PARTICLES
W
Cr
POLONIUM
IRRADIATED VOLUME
0
10 μ
SCALE OF CELL AND NEEDLE

FIGURE A.II-13

Irradiation of Part of the Cytoplasm of an Interphase Cell by Alpha Particles from a Polonium-Tipped Microneedle [20]

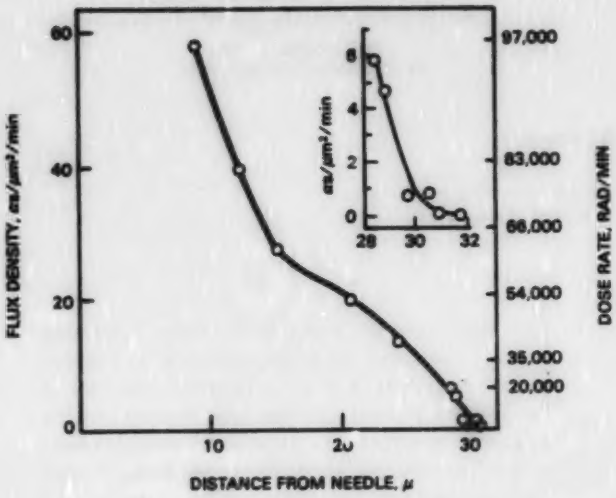


FIGURE A.II-14

Dose Rate, Rad/min, and Flux Density, Particles/μm²/min, Against Distance for a Typical Needle (inset: end of the range on a larger scale, showing the sharp cutoff) [20]

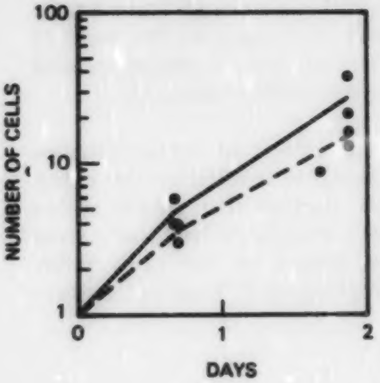


FIGURE A.II-15

Alpha-Irradiation of Cell Cytoplasm (Solid line—growth of three cells given cytoplasmic alpha irradiation; broken line—three similarly selected controls on the same coverslip; points give extreme ranges of counts) [20]

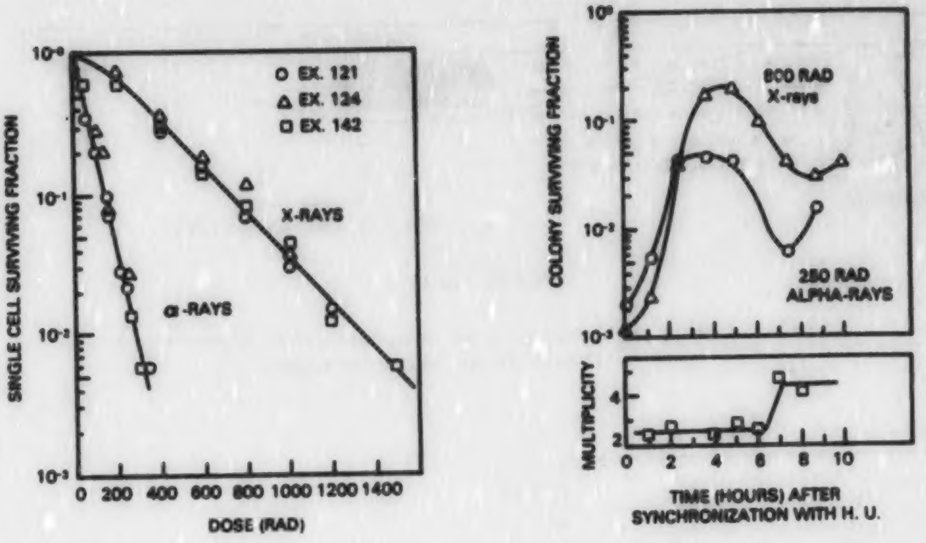


FIGURE A.II-16

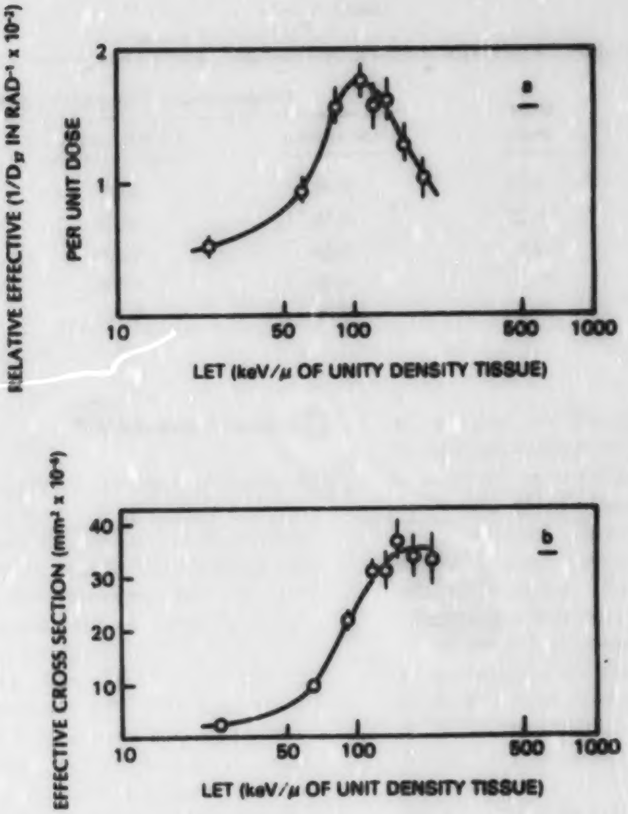
Survival Curves for Asynchronous Chinese Hamster
Cells Exposed to 210-keV X-rays or Alpha Particles [34]

He further calculates that at about 35 eV/ionization, the experimental data are compatible with a track core relative effectiveness of 10 to 15 ionizations (n) per 100 Å but that this is small compared to the effective cross sections calculated per particle (∿2-35 m²).

The implication is that "although the sensitive structure, or molecules, in the cell comprises a relatively large part of the cell or probably of the cell nucleus, damage to reproductive capacity is already produced if in a small part of this structure or of such a molecule a large amount of energy is deposited." His hypothesis that a given number of n or more ionizations is required in a certain small volume to initiate the chain of events resulting in death of a cell may be modified in such a way that the **total amount of damage** produced in a small volume must exceed a given minimum value and that this total damage is on the average produced by n ionizations.

The data on cell lethality *in vitro* following alpha irradiation as predominantly a nuclear event requiring a high ionization density is further supported by the observation of an efficient production of α-induced chromosomal aberrations. In a recent study by Vulpis [36] on human lymphocytes in culture, 2.5 MeV alphas (0.5 rad/min) produced a spectrum of aberrations similar to that following x-irradiation. The yield of aberrations was exponential between 3.5 and 17 rad of alphas and "saturated" at higher doses (Table A.II-2). Relative to x-rays, for example, the yield of dicentrics per cell (0.1 to 2.5 range) showed a reasonably constant RBE of about 23.

The data on the effects of alpha particles at the cellular level, as typified by the above studies, strongly suggest that single alphas traversing a cell's cytoplasm will likely have minimal, if any, impact on the cell's ability to survive and reproduce. If, however, a single



Energy (MeV)	LET (keV/µ of Unit Density Tissue)	D_{37}		Relative Effectiveness	
		Rad	Particles Per mm² (x 10^4)	Per Unit Dose ($^1/D_{37}$ in rad^{-1} x 10^{-2})	Per Particle (Cross Section in mm² x 10^{-6})
1.8	200 ± 40	97 ± 13	3.03 ± 0.41	1.03 ± 0.14	33.0 ± 4.4
2.5	166 ± 20	79 ± 9	2.98 ± 0.34	1.27 ± 0.14	33.6 ± 3.8
3.1	141 ± 15	62 ± 6	2.75 ± 0.26	1.61 ± 0.15	36.4 ± 3.5
3.6	123 ± 10	64 ± 7	3.25 ± 0.36	1.56 ± 0.17	30.8 ± 3.4
4.0	110 ± 10	57 ± 4	3.24 ± 0.23	1.75 ± 0.12	30.8 ± 2.2
5.2†	85.8 ± 10	64 ± 5†	4.66 ± 0.36	1.56 ± 0.12	21.4 ± 1.7
8.3†	60.8 ± 5	107 ± 12†	11.0 ± 1.2	0.93 ± 0.10	9.1 ± 1.0
26.8†	24.6 ± 2	197 + 30†	50 ± 7.6	0.51 ± 0.07	2.0 ± 0.3

FIGURE A.II-17

Mean Lethal Dose and Relative Effectiveness of α-particles for Impairment of the Proliferative Capacity of Cultured Human Cells [35]

TABLE A.II-2.

Chromosome Aberration Frequencies Induced by Thermal Neutrons in Human Lymphocytes [36]

Exposure Time (min)	Dose (rad)	Chromosomal Aberrations per Cell		
		Dicentrics	Centric Rings	Fragments
7.5	3.75	0.09	0.006	0.04
12.5	6.25	0.16	0.020	0.17
25.0	12.5	0.54	0.050	0.50
35.0	17.5	1.40	0.310	0.37
50.0	25.0	3.00	1.200	3.50

alpha particle traverses a cell nucleus (or its membrane) so that an ionization density of about 100 keV/μm is achieved, there is a high likelihood of irreparable molecular damage sufficient to kill the cell. There is compelling evidence that a surviving cell whose nucleus receives a "small" portion of the alpha track energy may have the opportunity to pass some nonlethal genetic lesion on to its progeny, and this possibility may influence the sequence of tissue events which leads to the induction of a tumor. Furthermore, if an ionizing event in a nucleus is not lethal, the cell may also have minimal opportunity for endogenous repair, thus causing efficient replication of the "lesion" in this special class of alpha-irradiated cells.

It is of further interest to speculate on the applicability of these high dose rate studies to a model in which a cell in its entire lifespan may encounter only a single alpha particle. The temporal distribution of dose in living tissue may produce very different quantitative estimates of effect and these may be difficult to derive solely on the basis of *in vitro* high dose rate studies. In particular, the spatial distribution of cells around a "hot particle", in comparison to the "uniform" distributions used in cell culture, might suggest a major sparing effect proportional to the frequency with which a single cell is traversed by multiple alpha particles. Insofar as cell killing may be related to cancer risk, the *in vitro* data would suggest that the radiation effect is greatest when the alpha flux is diffusely distributed.

Animal Experiments*

Clinical Responses to Inhaled Plutonium

Information on clinical responses to inhaled plutonium has been derived entirely from studies with experimental animals. (Chromosome aberrations have been observed in blood lymphocytes of workers contaminated with plutonium [37,38], but since these workers were probably also exposed to external radiation it is not clear that the aberrations were due to the alpha radiation from the plutonium.) Since the biological effects of inhaled plutonium have been reviewed in several recent reports [13,30,39-43], principal attention will be given to delayed effects here.

Clinical responses to inhaled plutonium are the result of alpha irradiation of the tissues in which plutonium is transported or deposited (primarily blood, lung, thoracic lymph nodes, liver, and bone). The time of onset and the magnitude of the response have been shown to be dose-dependent. The principal clinical responses to inhaled plutonium are shown in Table A.II-3, with the approximate minimum alveolar burdens of plutonium and tissue radiation doses observed to cause these effects in experimental animals. Extremely high doses of alpha radiation from plutonium cause severe hemorrhage and edema, resulting in early death due to massive destruction of

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*Prepared for the Committee's use by W. J. Bair

TABLE A.II-3

Clinical Responses to Inhaled Plutonium in Experimental Animals

	Approximate Minimal Dose Observed to Cause the Effect	
Biological Effect	**Inhaled Dose (μCi/g of lung)**	**Radiation Dose to Critical Tissue or Organ (rad)**
Lung Hemorrhage and Edema	0.5	15,000
Respiratory Insufficiency	0.02	1,800
Lung Fibrosis	0.005	∿200
Lymphopenia	0.001	(Critical tissue not known)
Lung Cancer	0.002	∿10 (rats) ∿1,000 (dogs)
Bone Cancer	0.01	3.6 (rats) 78 (dogs)

functional tissues. Lower doses may cause fibrosis and metaplasia severe enough to lead to respiratory insufficiency and eventual death.

Fibrosis may or may not be accompanied by metaplastic or neoplastic changes. Pulmonary neoplasia has been observed in rats at calculated cumulative radiation doses less than about 10 rad. However, so far the lowest calculated dose associated with pulmonary neoplasia in dogs is about 1000 rad. Whether neoplasia will occur at lower doses in dogs is not yet known, since low dose experiments have only been in progress for about five years. Osteogenic sarcoma has occurred in dogs at doses of about 78 rad and in rats at doses as low as 3.6 rad.

In dogs lymphocytopenia is so far the most prominent effect of plutonium deposition in lungs. The degree to which circulating lymphocytes are reduced and the time span between plutonium inhalation and lymphocyte reduction depend on the dose [44]. This is illustrated by the results from current studies of inhaled $^{239}PuO_2$ and $^{238}PuO_2$ in beagle dogs [44]. Figure A.II-18 shows the leukocyte levels in control beagle dogs and in dogs after inhalation of six levels of $^{239}PuO_2$. Lymphocytopenia occurred in the four highest dose groups and was related to the plutonium dose in both time of appearance after exposure and magnitude. The decrease in neutrophil levels was gradual and less pronounced than the decrease in lymphocytes. No differences occurred in either monocyte or eosinophil levels in plutonium-exposed dogs and no effects were seen in red cell levels.

The hematological changes in dogs exposed to $^{238}PuO_2$ are similar to those observed in dogs exposed to $^{239}PuO_2$, except that there is a greater decrease in neutrophil levels. This is probably the result of the translocation of ^{238}Pu to bone, which occurs more rapidly after inhalation of $^{238}PuO_2$ than after $^{239}PuO_2$.

The mechanism by which lymphocytopenia occurs is unknown, but it may be due to direct irradiation of lymphocytes circulating through the lungs in which plutonium is deposited. Whether the lymphocytopenia is related to the accumulation of plutonium in thoracic lymph nodes is not known, but lymphocytopenia has been observed in dogs before appreciable amounts of plutonium have appeared in the lymph nodes.

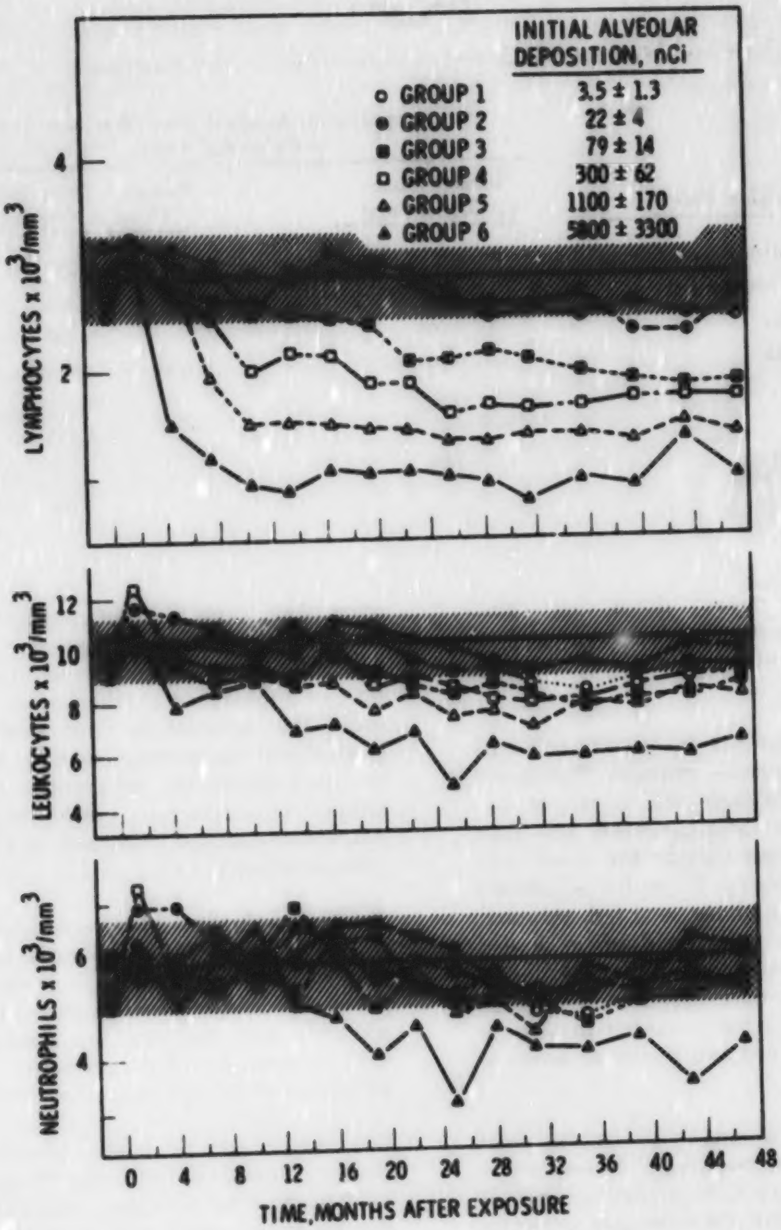

FIGURE A.II-18

Mean Lymphocyte, Leukocyte and Neutrophil Values from Dogs after Inhalation of $^{239}PuO_2$. (The shaded area represents mean values from age-related control dogs ± the mean 95% confidence interval) [44]

Neoplasia in Experimental Animals After Inhalation of Plutonium and Other Transuranics

Inhaled plutonium and other transuranics have been shown to cause pulmonary neoplasia and osteosarcoma in several experimental animal species. Pulmonary neoplasia is the dominant carcinogenic response when the plutonium is retained in the lung for a long period. Osteogenic sarcoma also occurs when inhaled plutonium is relatively soluble and is translocated to bone. Liver also accumulates plutonium translocated from respiratory tissues, but liver cancer has not been a common finding in studies of inhaled plutonium. Leukemia has rarely been observed in plutonium studies, although plutonium is transported in blood and deposited in lymphatic tissues and has been associated with other effects on blood elements, such as a reduction of lymphocytes and neutrophils [40].

The major experiments performed to date in which pulmonary neoplasia has been observed are summarized below.

Ammonium Plutonium-Pentacarbonate and Plutonium Citrate in Rats [45]. Plutonium citrate is relatively soluble and does not readily hydrolyze or form polymers. Therefore, inhaled plutonium citrate deposited in the lung is expected to be widely dispersed, rapidly translocated to bone and other tissues in the body, and excreted. Ammonium plutonium-pentacarbonate hydrolyzes, readily forming aggregates. Both compounds appear to have similar translocation characteristics. Thus, in this study the authors believed the total radiation dose to the lung would be comparable for these two plutonium compounds, but the distribution would be different (e.g., more localized in the case of ammonium plutonium-pentacarbonate). However, this difference was not documented in the report. Throughout the duration of the experiment autoradiograms showed plutonium aggregates associated with hemosiderin deposits. Quantitative descriptions of this aggregation were not provided by the authors for either plutonium citrate or ammonium plutonium-pentacarbonate.

The experiment involved 2232 rats, of which 376 were killed immediately after exposure to determine the initial lung burden. The characteristics of the aerosols were not published. The experimental design and results are given in Table A.II-4. The two plutonium compounds appeared to be equally effective at the lower dose in causing lung cancer. Differences may have occurred at doses above 500 rad.

Plutonium-239 Nitrate and Triacetate [46]. This experiment consisted of 1097 Wistar rats weighing 140-160 g. Solutions (0.03 mℓ) of plutonium nitrate (pH = 2), 0.01 N nitric acid (pH = 2) and sodium plutonyl triacetate (pH = 6.5) were given by intratracheal injection. From autoradiograms it was determined that both plutonium compounds were present for long times after administration as aggregates in macrophages in sclerotic areas of the peripheral lung, in interalveolar septas and beneath the pleura. Although the surfaces of the bronchi and lumens of the vessels were free of plutonium, the greatest numbers of large aggregates were in scar tissue in the hilar region and were associated with iron-containing pigment in connective tissue cells or extracellularly between collagen fibers.

Nitric acid alone caused an increased incidence of adenocarcinomas which was not observed in the rats which received lower levels of plutonium (Table A.II-5). Thus, if nitric acid had any effect on the induction of cancer by plutonium it was one of depressing the response, rather than enhancing plutonium carcinogenicity.

Intratracheally-injected plutonium increased the total incidence of pulmonary neoplasia but the response relative to dose was not as great as observed after inhalation of plutonium citrate and ammonium plutonium-pentacarbonate (Table A.II-4). The authors concluded that nitric acid scarring of the lung tissue was an indirect cause of neoplasia. However, there was no evidence that nitric acid enhanced the carcinogenic effect of plutonium.

TABLE A.II-4

Frequency of Pulmonary Tumors in Rats After Inhalation of Plutonium Citrate and Ammonium Plutonium-Pentacarbonate [45]

	Controls	Plutonium Citrate									
Number of Rats	258	23	12	94	39	113	105	31	203	120	157
Mean Survival Time (days)	570.8 ± 8.3	64.2 ± 2.1	69.3 ± 4.8	123.6 ± 9.0	220.7 ± 12.9	415.6 ± 11.8	463.6 ± 11.8	546.4 ± 22.3	544.9 ± 10.5	585.0 ±11.5	635.0 ±3.3
Initial Lung Content (μCi)	0	1.03	0.80	0.51	0.362	0.249	0.160	0.080	0.040	0.020	0.008
Dose (rad)	0	3820	3090	2370	1740	1390	852	467	234	117	47
Incidence of Tumors (%)											
All Pulmonary Tumors	6.6			2.2	28.2	47.9	40.9	48.5	25.6	18.3	15.9
Squamous Cell Carcinoma	--			2.2	7.7	16.8	7.6	9.7	1.5	--	3.2
Adenocarcinomas	0.39			--	--	3.6	14.3	16.1	5.4	2.5	1.3
Adenomas	1.17			--	20.5	23.0	15.2	6.5	10.8	8.3	3.2
Hemangiosarcomas	--			--	--	3.6	3.8	9.7	1.5	--	0.7
Lymphosarcomas	5.04			--	--	0.9	--	6.5	6.4	7.5	7.0
Total: Squamous Cell, Adenocarcinoma, and Hemangiosarcoma	0.39			2.2	7.7	24.0	25.7	35.5	8.4	2.5	5.2

	Controls	Amonium Plutonium-Pentacarbonate									
Number of Rats	258	12	23	69	22	126	83	126	91	101	48
Mean Survival Time (days)	570.8 ± 8.3	77.3 ± 5.6	77.8 ± 6.6	138.9 ± 9.6	247.4 ± 20.8	360.9 ± 11.1	484.3 ± 13.7	581.8 ± 11.4	583.9 ± 11.7	571.6 ± 16.1	570.9 ±20.9
Initial Lung Content (μCi)	0	1.46	0.77	0.45	0.35	0.245	0.15	0.040	0.020	0.008	0.004
Dose (rad)	0	7320	3900	2780	2140	1615	1065	497	186	80	41
Incidence of Tumors (%)											
All Pulmonary Tumors	6.6			7.7	9.0	44.4	78.4	63.2	35.2	19.8	16.7
Squamous Cell Carcinoma	--			--	4.5	11.9	14.5	9.5	5.5	1.0	--
Adenocarcinomas	0.39			4.6	4.5	7.9	24.6	7.7	3.8	1.0	--
Adenomas	1.17			3.1	--	19.8	30.1	17.3	18.7	7.9	4.2
Hemangiosarcomas	--					48	16.9	3.9	--	2.0	--
Lymphosarcomas	5.04			4.6	9.0		2.4	7.9	3.3	5.9	8.3
Total: Squamous Cell, Adenocarcinoma, and Hemangiosarcoma	0.39					24.6	45.9	38.0	13.2	6.0	4.2

TABLE A.II-5

Frequency of Pulmonary Tumors in Rats after Intratracheal Injection of ^{239}Pu Triacetate [46]

	Controls	^{239}Pu Triacetate	^{239}Pu Nitrate								
Number of Rats	248	52	42	94	110	87	93	96	93	93	89
Mean Survival Time (days)	672.7 ± 7.7	391.5 ± 17.1	586.2 ± 20	289.6 ± 8.7	417.5 ± 10	535.0 ± 15.1	599.4 ± 12.6	578.6 ± 15.7	586.7 ±17.0	628.0 ± 13.0	625.4 ± 15.3
Initial Lung Content (μCi)	0	1.0	HNO_3	1.0	0.42	0.01	0.048	0.031	0.01	0.0042	0.00042
Dose (rad)	0	1570	0	5855	2756	620	317	205	62	28	2.8
Incidence of Tumors(%)											
All Pulmonary Tumors	0	38.45	7.2	21.27	39.07	21.84	22.13	8.33	10.76	7.54	11.24
Squamous Cell Carcinoma		32.69	0	19.15	16.4	5.75	1.1	1.04	0	1.1	2.25
Adenocarcinomas		1.92	2.4	1.06	12.7	3.45	5.38	3.12	2.15	0	0
Adenomas		1.92	0	1.06	7.27	8.05	14.6	2.08	0	3.23	3.37
Hemangiosarcomas		1.92	0	0	0.9	4.6	1.1	0	0	0	0
Lymphosarcomas	5	0	4.8	0	1.8	0	0	2.08	8.6	3.23	5.62
Total: Squamous Cell, Adenocarcinoma, and Hemangiosarcoma		36.54	2.4	20.21	30.0	13.79	7.53	4.17	2.16	1.08	2.25

The effect of plutonyl triacetate is difficult to assess because there was only one dose group. Since the pH of the injected solution was more compatible with lung tissue than the 0.01 N nitric acid in which the plutonium nitrate was injected, there was probably less scarring due to chemical action. However, the neoplastic response was not less for plutonyl triacetate than for plutonium nitrate.

It is impossible to compare the heterogenicity of the distribution of plutonium and plutonium aggregates in the lungs of the rats in these two experiments; however, it is likely that intratracheal administration of plutonium nitrate solutions led to more nonuniformity than inhalation of plutonium citrate and ammonium plutonium-pentacarbonate. Since plutonium nitrate given by intratracheal injection was less effective than inhaled plutonium citrate and ammonium plutonyl pentacarbonate in causing pulmonary neoplasia, it does not appear that scarring of the lung by nitric acid or the greater aggregation of plutonium, which occurred in the case of intratracheal injection of plutonium nitrate, enhanced the carcinogenic effect of plutonium.

Inhaled Plutonium Nitrate and Ca-DTPA Treatment in Rats [47]. Male Wistar rats were exposed to aerosols of $^{239}Pu(NO_3)_4$ generated from a 0.27 N nitric acid solution. Beginning after 28 days the rats were treated for one hour at weekly intervals for six weeks by exposure to aerosols of calcium diethylenetriamine-pentaacetic acid (Ca-DTPA), a chelating agent given clinically to plutonium-contaminated human beings to increase the plutonium excretion rate. The amount of Ca-DTPA given the rats at each treatment was ∿5 mg/kg, approximately equivalent to the dose given human beings.

For long-term observation of biological effects the experiment was comprised of 261 rats in groups, as shown in Table A.II-6. Since Ca-DTPA treatment did not appear to influence the carcinogenic effect of plutonium, the incidence values were calculated for the combined groups of Ca-DTPA and sham-treated rats. In this experiment inhaled $^{239}Pu(NO_3)_4$ was very effective in causing pulmonary neoplasia. A 33% incidence was observed in the dose range of 36-100 rad and a maximum of 75% in the dose range of 1001-2000 rad. This response was much greater than that observed by Yerokhin et al. [46] with intratracheally-injected plutonium nitrate, also in Wistar rats. The difference in response may be due to the method of administration, since inhalation results in more uniform distribution of plutonium in the lungs than does intratracheal injection, or to the higher concentration of nitric acid in the solution from which Ballou generated his aerosol than in the solution given intratracheally by Yerokhin. The distribution of HNO_3 deposited in the rat lungs in the two experiments would also be different for the two routes of administration; inhaled HNO_3 would be more widely dispersed than HNO_3 given by intratracheal injection.

Inhaled $^{239}PuO_2$, $^{239}Pu(NO_3)_4$, and $^{238}Pu(NO_3)_4$ in Rats [48]. Sprague-Dawley S. P. F. rats were exposed to aerosols of $^{238}Pu(NO_3)_4$, $^{239}Pu(NO_3)_4$, and $^{239}PuO_2$. The normality of the nitric acid solutions from which the aerosols were generated has not been reported. The results are given in Table A.II-7. In this experiment, about half of the pulmonary tumors were bronchogenic carcinomas and about half were bronchiolo-alveolar carcinomas. Plutonium-239 nitrate appeared to be more effective than $^{238}Pu(NO_3)_4$. Both results agreed better with the results of Ballou's inhaled $^{239}Pu(NO_3)_4$ experiment than with Yerokhin's intratracheally-injected $^{239}Pu(NO_3)_4$.

Inhaled $^{239}PuO_2$ resulted in a high incidence of lung cancer at doses ranging from 165 to 1300 rad. Over this dose range the tumor response appeared to be independent of dose. This may be due to the relatively small numbers of animals in each dose group. At comparable doses $^{239}Pu(NO_3)$ appeared to be more effective than $^{239}PuO_2$, while the response to $^{238}Pu(NO_3)_4$ was similar to that observed for $^{239}PuO_2$.

Inhaled ^{241}Am Oxide and Nitrate [48]. Sprague-Dawley rats were given single exposures to aerosols of ^{241}Am oxide and ^{241}Am nitrate (Table A.II-8). Americium-241 oxide is relatively soluble and is translocated from the lung more rapidly than PuO_2. Although information about the distribution of these materials in

TABLE A.II-6

Lung Tumors in Rats After Inhalation of $^{239}Pu(NO_3)_4$ and Treatment with Ca-DTPA [47]

Dose Range (rad)	Number of Rats	Mean Number Days at Risk	Rats with Lung Tumors	
			Number	%[b]
36-100	5 (1)[a]	603 (888)	1 (1)	33
101-300	13 (3)	555 (546)	5 (1)	38
301-500	16 (7)	657 (608)	5 (3)	35
501-1000	8 (5)	714 (699)	6 (2)	62
1001-2000	1 (3)	975 (641)	1 (2)	75
Ca-DTPA	70 (30)	604 (591)	1 (0)	1
Control	99	677	0	0

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[a] Numbers in parentheses are for rats sham treated with Ca-DTPA.
[b] Percentages calculated for combined Ca-DTPA and sham-treated rats.

TABLE A.II-7

Lung Tumors in Rats after Inhalation of $^{239}PuO_2$, $^{239}PuO(NO_3)_4$ and $^{238}Pu(NO_3)_4$ [48]

Treatment	Pu Deposited in Lung (μCi)	Lung Dose (rad)	Mean Survival Time (days)	Number of Rats	Lung Tumor Incidence: No. of Rats with Tumor	%
$^{239}PuO_2$	0.045	165	735	14	7	50
	0.050	200	720	9	3	33
	0.080	265	700	8	5	62
	0.095	340	650	18	13	72
	0.135	550	550	10	6	60
	0.170	650	525	16	9	56
	0.350	1300	375	33	22	66
$^{239}Pu(NO_3)_4$	0.240	560	550	18	16	89
$^{238}Pu(NO_3)_4$	0.315	780	450	8	4	50

TABLE A.II-8

Lung Tumors in Rats after Inhalation of ^{241}Am Oxide and Nitrate [48]

^{241}Am Compound	^{241}Am Deposited in Lung (μCi)	Lung Dose (rad)	Mean Survival Time (day)	Number of Rats	Lung Tumor Incidence: No. of Rats with Tumor	%
Oxide	0.055	50	750	5	1	20
	0.27	250	700	9	5	55
	0.50	450	620	9	5	55
	0.87	800	500	4	2	50
Nitrate	0.13	170	730	12	2	16
	0.24	290	675	19	3	16
	0.64	830	450	20	15	75
	1.0	1300	375	17	10	60

the lung has not been reported, the oxide might result in less uniformity than the nitrate. However, this difference would be short-lived, as the oxide is dissolved and mobilized within the lungs and translocated to other tissues. Since the nitrate experiment was comprised of more rats than the oxide experiment, the incidence data are more meaningful and comparison with the oxide experiment may be misleading. The $^{241}AmO_2$ appeared to be more effective in causing pulmonary neoplasia at low doses but not at high doses. As in the PuO_2 experiment, the $^{241}AmO_2$ appeared to be relatively independent of dose in causing pulmonary neoplasia.

Inhaled ^{238}Pu [49]. Female Sprague-Dawley rats were given a single exposure to a ^{238}Pu aerosol generated from a physiological saline suspension solution of ^{238}Pu prepared from the water supernatant of aged ^{238}Pu crushed microspheres further ground with mortar and pestle. Electron micrographs showed the presence of amorphous-like material rather than the highly dense, sharply defined particles present in suspensions and aerosols of PuO_2. Autoradiograms showed few aggregates in lung samples collected one day after exposure. The alpha tracks were randomly distributed throughout the lung. After a year the small amount of ^{238}Pu remaining was associated with hemosiderin-like pigment granules in peribronchiolar and perivascular regions of the lungs. The incidences of pulmonary neoplasia observed in these rats are shown in Table A.II-9.

An increased incidence of neoplasia, mostly bronchiolo-alveolar carcinomas, was observed at 9 rad. However, the 6.6% incidence at 9 rad was not significantly different from the 1.1% incidence in the control group. At a dose of 32 rad, the tumor incidence was 20%, which was significantly different from the controls at the 99.9% confidence level. The author attributed the high tumor incidence at these low doses to the diffuse distribution of the ^{238}Pu in the lungs, compared with PuO_2. The results from this experiment are fairly compatible with the results obtained by Ballou with $^{239}Pu(NO_3)_4$ [47] and Lafuma with $^{238}Pu(NO_3)_4$ [48].

PuO_2 in Lung After Intraperitoneal Injection [50]. In a study of PuO_2 given to female Sprague-Dawley rats by intraperitoneal injection it was found that some of the Pu particles were transported to the lungs and deposited in capillaries of the alveolar septae randomly throughout the lungs. Autoradiography indicated the median diameter of these particles to be 0.3 μm. In addition to plutonium, one group of animals was given benzo(a)pyrene and another group asbestos. However, the presence of these substances in the lungs was not confirmed.

There was little evidence of pulmonary pathology in these rats, even though the dose to the lungs of one group was estimated to be as high as 600 rad (Table A.II-10). Pulmonary neoplasia was observed in only one rat. A bronchiolo-alveolar carcinoma was found in one rat 823 days after intraperitoneal injection of 72 nCi PuO_2. Since pulmonary neoplasia is occasionally seen in the control rats, <1%, the finding of one neoplasia cannot unequivocably be attributed to ^{239}Pu.

The author concluded that the lack of a significant neoplastic response in this experiment was due to the immobilization of the PuO_2 particles in the lung capillaries and consequent irradiation of a limited number of epithelial cells in the lungs, fewer than would be the case with inhaled plutonium.

TABLE A.II-9

Lung Tumors in Rats after Inhalation of ^{238}Pu [49]

Initial Alveolar Deposition (nCi)	Lung Dose (rad)	Number of Rats	Tumor Incidence	
			No. of Rats	%
Control	0	92	1	1.1
5	9	30	2	6.6
18	32	30	6	20
207	375	32	8	25

TABLE A.II-10.

Effects of Plutonium Deposited in Lung After Intraperitoneal Injection of PuO_2 in Rats [50]

$^{239}PuO_2$ (μCi)	Number of Rats	Survival Time (days)	^{239}Pu in Lung (% of Injected Dose)	Lung Dose (rad)	No. of Tumors
Controls	108		—	—	0
2.9	35	200-300	0.39 ± 0.22	600	0
0.36	38	200-500	0.21 ± 0.13	40	0
0.072	36	200-500	0.33 ± 0.29	10	1
0.36 + benzo(a)pyrene	18	200-500	1.5 ± 0.94	170	0
0.072 + asbestos	24	200-500	0.13 ± 0.11	20	0

Intratracheal Injection of ^{253}EsCl [51]. Einsteinium is an alpha-emitting (6.6 MeV) radionuclide with a half-life of 20.5 days. Thus, it is capable of delivering a dose of alpha radiation over a relatively short period of time compared with the other transuranics and with ^{210}Po, which has a half-life of 138 days.

Einsteinium-253 chloride in 0.01 N HCl (0.5 mℓ) was given by intratracheal injection to male Wistar rats for long-term observation of biological effects. Because of the small mass of einsteinium present (the specific activity of ^{253}Es is ~4 x 10^{-11} g/μCi), and especially the method of administration, the distribution of the einsteinium within the lung was probably limited. The results are shown in Table A.II-11.

The incidence of pulmonary neoplasia was 4% in rats with a lung dose of 38 rad and 12.5% in rats receiving 1900 rad. It is highly probable that the peak tumor response is somewhere between these two doses. However, these results are more comparable to those observed with intratracheally administered $^{239}Pu(NO_3)_4$ (Table A.II-5) than to those observed in experiments where the radionuclide was given by inhalation.

TABLE A.II-11.

Lung Tumors in Rats After Intratracheal Instillation of ^{253}EsCl [51]

^{253}EsCl Deposited in Lung (μCi)	Lung Dose (rad)	Mean Survival Time (days)	Number of Rats	Lung Tumor Incidence	
				Number of Rats with Tumors	%
Control (0.01 N HCl)		724	43	0	0
0.05	38	707	48	2	4
2.5	1900	475	48	6	12.5
12	9800	181	29	0	0

Inhaled $^{239}PuO_2$ in Dogs [52]. Beagle dogs were given a single exposure to aerosols of $^{239}PuO_2$. Thirty-five were held for lifetime observation and 5 were sacrificed at times after 800 days for determination of the tissue distribution of the inhaled ^{239}Pu. Data for the 35 dogs are given in Table A.II-12. Of these dogs, 27 developed primary pulmonary neoplasia, 6 died of pulmonary fibrosis with no evidence of neoplasia, one died of cardiovascular disease and another of encephalitis.

The latter two deaths did not appear to be related to the plutonium exposure. All dogs with pulmonary neoplasia also showed extensive pulmonary fibrosis at time of death. All dogs with pulmonary neoplasia had bronchiolo-alveolar carcinomas (histopathology is not complete on 3 dogs). Some dogs had more than one tumor but it is not known whether they were all primary tumors or metastasis from a single primary tumor. Several dogs had additional neoplasms, as shown in Table A.II-12 [53]. Radiographs showed that the tumors originated in the lung periphery. Autoradiographs of lung sections taken from these and other dogs showed PuO_2 had accumulated in subpleural regions of the lungs in apparent association with the subpleural lymphatics and, to a lesser extent, in peribronchiolar and periovascular regions. The location of the PuO_2 in the lungs appeared to coincide with the peripheral origin of the tumors. Although autoradiographs seldom showed high concentrations of ^{239}Pu within the tumor mass, it was generally observed that relatively large accumulations of ^{239}Pu occurred in fibrotic regions near the tumors.

Because this experiment involved relatively high doses of plutonium, a large fraction of the lung tissue was exposed to alpha irradiation. This distribution of radiation dose was enhanced by mobilization of the plutonium in the lungs by macrophages, by transport in the lymphatics, and by slow solubilization. However, mobilization also caused plutonium to accumulate in the subpleural and peribronchiolar regions, with the result that these regions of the lung received relatively high doses. The results demonstrate the peripheral origin of $^{239}PuO_2$-induced neoplasia in the lungs of dogs.

$^{239}PuO_2$ and Asbestos [54]. Female Sprague-Dawley rats were given a single intratracheal injection of 0.9 mg chrysotile asbestos, 29 nCi $^{239}PuO_2$ or 0.9 mg asbestos and 51 nCi $^{239}PuO_2$ in saline. Asbestos tended to sequester the PuO_2 in the peribronchiolar regions of the lungs and signficantly reduced the rate of PuO_2 clearance from the lungs. The asbestos tended to increase inflammation and scarring of the lung tissue. Thus, the PuO_2 in the presence of asbestos was located in areas of greater scar formation than was the PuO_2 in the lungs of rats which received no asbestos. The mean cumulative radiation doses were 425 rad to the lungs of rats given PuO_2 and 1200 rad to the lungs of rats given PuO_2 plus asbestos. The rates of mortality were similar in the two groups. Table A.II-13 shows that there was no difference in the incidences of pulmonary neoplasia in the PuO_2 and PuO_2 plus asbestos rats, even though the radiation dose was three times greater in the latter group.

The results of this experiment demonstrate that the effectiveness of $^{239}PuO_2$ is not enhanced by aggregation in scar tissue in lungs; rather, they suggest a greater effectiveness when the $^{239}PuO_2$ is more widely distributed.

^{210}Po Given by Intratracheal Injection to Hamsters [55,56]. Syrian golden hamsters were given intratracheal administrations of ^{210}Po in saline alone or with hematite. In this experiment the hematite tended to cause aggregation of the ^{210}Po, while ^{210}Po administered in saline was more uniformly distributed throughout the lung. It is probable that intratracheal administration of the ^{210}Po resulted in less uniform distribution than would have occurred had the ^{210}Po been given by inhalation. The results of these series of experiments are given in Table A.II-14 and Figure A.II-19. Included in Figure A.II-19 are data from an earlier experiment in which rats were exposed to aerosols of ^{210}Po in saline [57].

Neoplasia was not observed in the control hamsters or those given hematite alone. In rats given ^{210}Po alone or with hematite the incidence of pulmonary neoplasia ranged from 8 to 9%. At low doses there does not appear to be any difference in the effectiveness of ^{210}Po for inducing neoplasia, whether it is given alone or with

TABLE A.II-12.

Dog Mortality and Distribution of Inhaled $^{239}PuO_2$ [53]

Dog Number	Survival (days)	Lesion	Alveolar Deposit. (μCi)	Final Body Burden (μCi)	Percent of Final Body Burden: Lungs	Thoracic Lymph Nodes	Liver	Skeleton	Abdom. Lymph Nodes	Spleen	Lung Tumors	Lung Dose (rad)[a]
1 182F	855	F	3.3	2.7	74	21	2	1	—	—		4400
2 184F	933	F	3.0	2.5	75	17	5	1	—	—		4800
3 272M	988	F	3.6	2.9	63	17	14	4	2.0	—		4300
4 215F	1151	FT	1.8	1.4	50	42	2	4	—	0.5	B-A	2700
5 83F	1184	FT	2.2	1.8	59	28	6	2	0.9	0.1	B-A	3800
6 268F	1202	E	1.4	1.1	46	25	20	3	—	—		2800
7 173F	1339	FT	2.6	2.1	46	48	2	2	—	—	B-A	6200
8 106F	1357	FT	3.3	2.7	50	37	6	2	—	—	B-A	6700
9 183F	1379	F	1.1	0.9	52	38	6	3	—	—		2000
10 180F	1446	F	1.7	1.4	42	49	5	3	—	—		3600
11 76F	1549	F	1.8	1.4	47	45	3	4	—	—		3700
12 246M	1623	FT	2.3	1.8	55	24	16	3	—	—	B-A, Bronchial carcinoma, hemangiosarcoma	2800
13 259M	1629	FT	1.2	1.0	55	23	15	6	—	—	B-A	2500
14 255F	1635	FT	1.2	1.0	42	24	26	3	3.7	1.0	B-A, capillary hemangioma, mesothelioma	2200
15 213F	1720	FT	1.5	1.2	49	27	15	5	—	—	B-A	3700
16 216F	1823	FT	0.6	0.5	51	26	15	7	0.7	0.3	B-A	1900
17 85F	2015	FT	1.4	1.1	36	30	21	6	5.8	0.7	B-A	3400
18 258M	2048	FT	1.8	1.4	35	37	19	4	4	0.4	B-A, Squamous Cell	3300
19 86F	2050	C	0.4	0.3	37	48	6	5	—	—		970
20 281	2211	FT	2.2	1.7	30	44	15	5	4	0.2	B-A, Epidermoid	4200
21 81F	2229	FT	1.2	0.9	23	54	19	4	—	—	B-A (oat cell) mesothelioma (1)	2500
22 249M	2341	FT	1.2	1.0	21	32	32	6	8	0.7	B-A (2)	2300
23 283	2356	FT	0.9	0.8	26	29	23	12	7	1.2	B-A, Mesothelioma (2)	2400
24 212F	2367	FT	1.0	0.8	53	39	3	2	—	—	B-A	1900
25 266F	2412	FT	0.8	0.7	14	41	32	7	3	1.2	B-A, Epidermoid (3)	1700
26 273M	2565	FT	1.8	1.5	7	56	21	5	9	0.6	B-A	2700
27 278M	2792	FT	1.0	0.8	14	41	23	10	10	1.4	B-A, Epidermoid, Squamous cell car.	1900
28 254	2909	FT	0.8	0.6	21	45	21	5	6	0.7	B-A	2000
29 1F	3079	FT	0.7	0.6	9	56	21	7	6	1.0	B-A (3)	1700
30 109F	3313	FT	0.6	0.4	13	56	16	6	7	0.6	B-A	1600
31 252M	3441	FT	0.58	0.46	24	36	22	9	6	0.7	B-A, Epidermoid, Oat Cell, Squamous Cell	1700
32 93F	4068	FT	0.15	0.12	26	57	8	6	0.1	0.1	B-A (3)	956
33 277	3664	FT	0.19	0.15	15	24	31	9	17.0	2.6	?	987
34 284	3537	FT	—	—	—	—	—	—	—	—	?	—
35 267	3676	FT	0.86	0.67	11	18	61	6	1.6	1.7	?	2300

T - Pulmonary Tumor; F - Pulmonary Fibrosis and Metaplasia; C- Cardiovascular; E- Encephalitis; B-A - Bronchiolo-Alveolar Carcinoma

Other Tumors: (1) Lymphagiosarcoma in thoracic lymph nodes (2) Hemangiosarcoma in thoracic lymph node (3) Mammary gland adenocarcinoma

[a] Cumulative dose based on normal lung weight = 1.1% body weight. Retention half time for Pu in lung calculated for each dog based on final whole body burden = alveolar deposition x [illegible].

TABLE A.II-13.

Neoplastic Response of Lung to Intratracheally Instilled Asbestos, $^{239}PuO_2$ or Asbestos Plus $^{239}PuO_2$ [54]

Group	Number of Animals	Incidence of Pulmonary Tumors, % Adenocarcinoma	Squamous Carcinoma	Sarcoma	Total
Saline	26	0	0	0	0
Asbestos	22	4	0	4	9
$^{239}PuO_2$	22	21	11	0	32
$^{239}PuO_2$ Plus Asbestos	27	21	0	4	25

TABLE A.II-14.

Lung Tumors in Hamsters After Intratracheal Instillation of ^{210}Po [55,56]

Group	Lung Dose (rad)	Number of Rats Autopsied	Number of Rats with Tumor	Tumor Incidence (%)	Ref.
Control (no instillation)	0	60	0	0	55
Contrul - hematite (3 mg)[a]	0	34	0	0	55
^{210}Po (0.2 μCi) in saline + hematite (3 mg)[a]	5000	35	34	97	55
^{210}Po (0.2 μCi) in saline + hematite (3 mg)[b]	2000	37	25	68	55
^{210}Po (0.01 μCi) in saline + hematite (3 mg)[a]	300	32	17	53	55
Benzo(a)pyrene (3 mg) + hematite (3 mg)[a]	0	39	24	62	55
Benzo(a)pyrene (0.3 mg) + hematite (3 mg)[a]	0	37	3	8	55
^{210}Po (0.005 μCi) + hematite (3 mg)[a]	300	32	17	53	56
^{210}Po (0.00125 μCi) + hematite (3 mg)[a]	75	82	10	12	56
^{210}Po (0.00025 μCi) + hematite (3 mg)[a]	15	83	9	11	56
^{210}Po (0.1 μCi)[b]	1500	38	22	58	56
^{210}Po (0.00125 μCi)[a]	55	101	9	9	56

[a] 15 weekly instillations
[b] 7 weekly instillations

hematite. Compared with the earlier work of Yuile, inhaled ^{210}Po in rats was less effective than the intratracheally-injected ^{210}Po in hamsters (Figure A.II-19). This is in contrast to the results with $^{239}Pu(NO_3)_4$ in rats, where intratracheal injection appeared to be much less effective than inhalation of $^{239}Pu(NO_3)_4$.

Plutonium Microspheres Given Hamsters by Intravenous Injection [58,59]. To determine whether the lung is susceptible to tumor induction by isolated alpha-emitting particles, 10 μm ceramic microspheres were administered by intravenous injection to Syrian golden hamsters. Various quantities of ^{239}Pu or ^{238}Pu microspheres of varying specific activity (Table A.II-15) were administered to over 2300 hamsters. In addition, about 700 control hamsters were given either none; 2,000; 4,000; 10,000; 100,000; or 500,000 nonradioactive microspheres.

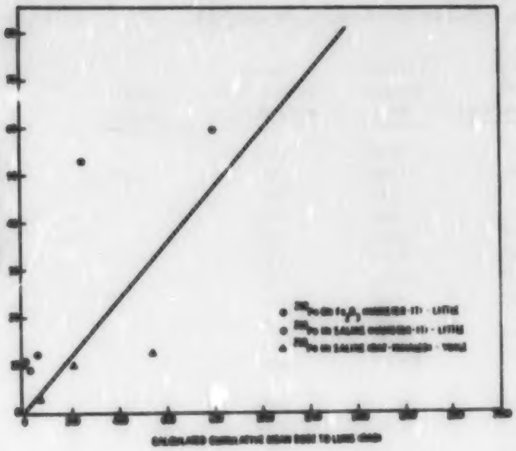

FIGURE A.II-19

Lung Cancer after Inhalation or Intratracheal Instillation of ^{210}Po

Results of this experiment are available from all but two groups of hamsters. Only four deaths from neoplastic disease have occurred. One animal that received 2000 microspheres (0.84 nCi) developed a hemangiosarcoma in the left lung and another developed a well circumscribed adenoma in the left lung. Two mucinous adenocarcinomas occurred in hamsters that received 6000 microspheres (354 nCi).

This experiment indicates that the hamster lung is not very susceptible to tumor induction by isolated plutonium particles deposited in the capillaries. The results confirm an earlier, smaller experiment with rats given plutonium microspheres by the same technique in which no neoplasia was observed. The results also agree with the experiment of Sanders in which $^{239}PuO_2$ particles deposited in lungs of rats following intraperitoneal injection failed to cause pulmonary neoplasia.*

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*On July 29, 1976 additional information was received on this study from Dr. Ernest C. Anderson at Los Alamos Scientific Laboratory.

Summary of Lung Tumor Incidence (LASL Data on Syrian Hamsters)

Specific Activity (pCi/sphere)	Number of Spheres	Lung Burden (μCi)	Approximate Dose[a]	Tumors / Animals	Incidence (% ± S.D.)	BAL[b] Animals	Incidence (% ± S.D.)
"DIFFUSE" EXPOSURES (greater than 25% of lung mass exposed)							
Intratracheal sol., ^{210}Po							
N.A.[c]	N.A.	0.12[d]	1-2 krad total	14/47	30 ± 8	12/47	24 ± 7
Intravenous spheres, ^{238}Pu							
2	70,000	0.14	13 krad/yr	17/163	10 ± 3	85/163[e]	32 ± 5
Intravenous spheres, ^{147}Pm							
450	50,000	22.0	28 krad/yr	12/54	22 ± 6	16/54	30 ± 7
LOCALIZED EXPOSURES (less than 3% of lung mass exposed)							
Intravenous spheres, ^{238}Pu							
60	6,000	0.36	30 krad/yr	2/148	1 ± 1	3/148	2 ± 1
60	2,000	0.12	10 krad/yr	0/72	0 ± 1	0/72	0 ± 1
13	2,000	0.03	2 krad/yr	0/70	0 ± 1	0/70	0 ± 1
4	6,000	0.02	2 krad/yr	0/154	0 ± 0.5	9/154	6 ± 2
CONTROLS							
				3/220	1.4 ± 0.8	1/220	0.5 ± 0.5

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[a] Total energy/total lung mass.

[b] Bronchiolar adenomatoid lesion; regardless of whether graded 1+, 2+, 3+.

[c] N.A. = not applicable.

[d] Maintained by weekly instillations for 7 weeks.

[e] Low grade BAL 1 to 2+.

*In this table the tumor incidence observed in hamsters in which the lungs received relatively diffuse alpha irradiation exposures is compared with the tumor incidence in hamsters given ^{238}Pu microspheres which irradiated less than 3% of the lung mass. A 10-30% tumor incidence is observed in the hamsters which received relatively diffuse radiation exposure, compared with only 1% in the group of hamsters that received ^{238}Pu microspheres. No tumors were found in three other groups. This is taken by the Los Alamos staff as conclusive evidence that highly localized alpha irradiation of the lungs is less effective in causing lung tumors than more diffuse alpha irradiation. The same conclusions can be drawn from the incidences of bronchiolar adenomatoid lesions. It should be noted that the ^{238}Pu microspheres in all four groups qualify as "hot particles" according to Tamplin and Cochran's definitions, in that all were above 0.07 and 0.6 pCi/particle.

TABLE A.II-15

Exposures of Hamsters to Intravenous Plutonium Microspheres [58]

Date of Exposure		Number of Animals	Spheres per Animal	Specific Activity (pCi per sphere)	Lung Burden (nCi)	Mean Survival Time (days of age[a])	Other Insults
1971	May	69	2,000	0.07	0.14	630	
	May	71	2,000	0.22	0.44	795	
	May	74	2,000	0.91	1.82	765	
	June	71	2,000	0.42	0.84	670	
	June	71	2,000	4.30[b]	8.60	635	
	June	71	2,000	13.30[b]	26.00	620	
	June	72	2,000	59.00[b]	118.00	650	
	Aug	71	2,000	2.10[b]	4.20	720	
	Aug	47	10,000	0.22	2.20	630	
	Nov	154	6,000	4.30[b]	26.00	720	
	Dec	148	6,000	59.00[b]	354.00	615	
1972	Feb	142	6,000	0.22	1.30	695	
	July	20	1,600,000	0.07	112.00	715	
	July	34	300,000	0.42	126.00	655	
	Dec	30	6,000	8.90[b]	53.00	(350)	Cytoxin
1973	April	109	60,000	0.91	55.00	490	
	April	107	80,000	8.90[b]	710.00	395	
	April	102	80,000	2.10[b]	168.00	515	
	May	104	80,000	0.22	18.00	680	
	June	37	400,000	0.42	170.00	505	
	June	109	150,000	0.06	9.00	455	
	July	97	500,000	0.03	15.00	470	
	July	44	50,000	0.91	45.00	440[c]	
	Oct	26	900,000	0.016	14.00	480	
	Oct	15	500,000	0.016	8.00	395	
	Nov	53	40,000	0.06	2.40	385	
	Nov	52	20,090	0.06	1.20	450	
1974	Jan	52	20,000	0.19	3.80	390	
	Jan	51	40,000	0.19	7.60	385	
	Jan	60	60,000	1.60	96.00	455	$C_2F_3Cl_4$
	May	76	60,000	2.10[b]	126.00	d	Zymosan
	May	71	30,000	0.19	11.00	d	Zymosan

[a] Animals exposed at age 100 days.

[b] Plutonium-238; all others contain ^{239}Pu.

[c] Weanlings exposed at age 30 days.

[d] No data yet available.

Inhaled $^{238}PuO_2$, $^{239}PuO_2$, and $^{244}CmO_2$ in Rats [60]. The carcinogenic response to inhaled $^{238}PuO_2$, $^{239}PuO_2$, and $^{244}CmO_2$ was compared in about 830 female PSF Wistar rats. The experiment included 188 controls. The rats were given a single exposure to the aerosol and observed for the duration of their life span (Table A.II-16).

The AMAD ranged from 1.2 to 2.6 μm for $^{238}PuO_2$, 1.7 to 3.4 μm for $^{239}PuO_2$, and 0.7 to 1.3 μm for $^{244}CmO_2$. Autoradiographs showed that at doses above 10 nCi, $^{238}PuO_2$ and $^{239}PuO_2$ were concentrated in subpleural and peribronchiolar regions of the lungs within several months after exposure. However, single alpha tracks in the $^{244}CmO_2$ animals suggested a much more diffuse distribution at all dose levels except for occasional aggregates in macrophages and hemosiderin. Particles were still present in $^{238}PuO_2$ and $^{239}PuO_2$ rats two years after exposure and were concentrated in subpleural regions of the lung and less frequently in peribronchiolar regions. More than half the pulmonary neoplasias observed were bronchiolo-alveolar adenocarcinomas. About a third were squamous cell carcinomas, occurring mostly in plutonium rats at the higher doses. Six hemangiosarcomas were seen in ^{239}Pu rats.

TABLE A.II-16

Pulmonary Neoplasia in Rats After Inhalation of $^{238}PuO_2$, $^{239}PuO_2$ or $^{244}CmO_2$ [60]

$^{238}PuO_2$*			$^{239}PuO_2$*			$^{244}CmO_2$		
Lung Dose (rad)[a]	No. of Rats	Tumor Incidence (%)	Lung Dose (rad)[a]	No. of Rats	Tumor Incidence (%)	Lung Dose (rad)[a]	No. of Rats	Tumor Incidence (%)
0	50	0	0	48	0	0	20	0
<10	118	2.5	<10	134	1.5	0.4	57	1.8
26 ±11	50	2.0	27 ± 12	51	7.8	6.0	61	3.3
56 ±11	33	9.1	78 ± 17	26	34.6	32.0	54	11.1
153 ± 81	34	5.9	255 ±132	38	44.7[b]	710.0	43	32.6
1720 ± 990	27	48.1[b]	680 ±120	16	31.3	1600.0	24	0
8340 ± 3240	6	100.0[b]	2100 ±1210	18	66.7[b]			
∿10,000	26	19.2[b]	∿10,000	15	46.7[b]			

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[a] Cumulative dose to 620 days postexposure: mean and standard deviation

[b] Significantly greater from controls at $P < 0.05$ level

*Data shown here were updated by Dr. Sanders from that appearing in the reference cited.

Pulmonary neoplasia was observed in groups of rats which received lung doses somewhat less than 10 rad. However, statistically significant increases of tumor incidence occurred only at higher doses. Of particular interest in this experiment is the apparently greater carcinogenic effectiveness of $^{239}PuO_2$ than $^{238}PuO_2$ at comparable doses. Since both plutonium isotopes were present as particles in the lungs, the difference in their effectiveness may be due to a difference in distribution of the absorbed energy. Because the specific activity of ^{238}Pu is 280 times greater than that of ^{239}Pu, if the particles of both are equivalent in size, one might expect equivalent radioactive quantitities of ^{238}Pu to be distributed among 280 fewer particles than for ^{239}Pu. Thus, all other factors being equal, a specific amount of ^{239}Pu might be expected to irradiate more cells than an equivalent amount of ^{238}Pu. The same explanation might also apply to the ^{244}Cm; however, the results are still incomplete.

The results of this experiment with $^{238}PuO_2$ contrast markedly with Sanders' previous experiment with "nonparticulate" ^{238}Pu, in which a statistically significant increase in lung cancer incidence (20%) occurred at 32 rad (Table A.II-9).

Other Studies

A number of animal studies which bear on the hot particle issue are in progress at several laboratories. While these studies are not sufficiently complete to draw conclusions of a quantitative nature, some of the preliminary data should be mentioned.

Ballou et al. [61] are studying the late effects of inhaled $^{238}Pu(NO_3)_4$, $^{239}Pu(NO_3)_4$, and $^{253}Es(NO_3)_3$ in about 1,000 male Wistar rats. Preliminary results indicate that the number of lung tumors in these rats which inhaled relatively soluble transuranic compounds greatly exceeds the number of skeletal tumors. Also, ^{253}Es, which has a very short half-life of 20.5 days, appears to be less effective in causing cancer than the much longer half-life ^{238}Pu and ^{239}Pu. This suggests a possible dose rate effect. Ballou [62] is also conducting a similar experiment with $^{241}Am(NO_3)_3$. Comparison of the results of these experiments with relatively soluble transuranics with the results from the experiments with insoluble transuranics will provide information relevant to the hot particle issue.

Two current studies of inhaled transuranic compounds in Syrian hamsters at Battelle, Pacific Northwest Laboratories [63] and at the Lovelace Foundation Inhalation Toxicology Research Institute [64] are of special interest to the general problem of the toxicity of inhaled radionuclides. Sanders [63] at Battelle has seen only three malignant lung tumors in about 300 hamsters after inhalation of $^{238}PuO_2$ or $^{239}PuO_2$. Mewhinney and Hobbs [64] at Lovelace have not reported any malignant lung tumors in experiments with about 2,500 hamsters which were exposed to Pu or Am aerosols; however, it must be noted that some of these experiments have not been in progress very long. Nevertheless, the data from both laboratories are adequate to suggest that Syrian hamsters are much less susceptible to the carcinogenic properties of inhaled alpha-emitting transuranics than rats. These negative results with hamsters are also in contrast to the high incidences of lung tumors in hamsters reported in the polonium intratracheal injection experiments at Harvard [55,56]. The reason for this difference is not known, but it may be related to the mode of administration of the radionuclide; i.e., a single inhalation of the transuranics as opposed to multiple intratracheal injections of polonium.

Conclusions

Experiments with animals have demonstrated that alpha-emitting radionuclides deposited in lungs have carcinogenic properties. Both particulate as well as less particulate radiation sources have been found to cause pulmonary neoplasia in rodents and dogs. None of these experiments have indicated that the transuranic alpha-emitting radionuclides are far more effective in causing lung cancer when the radiation dose to lung tissue is delivered by particulate, as compared to less particulate, sources.

Recently, attempts have been made to describe mathematically the relevant experimental animal data [65,66]. Because the data exhibit a wide range even within an experiment, it is not possible to argue for any particular dose-response relationship. However, a linear model was used in an analysis of the rat data [67]. Only data from groups of animals for which there was not an appreciable shortening of lifespan were used in the analysis; thus, only data for doses less than about 800 rad were included. The results are summarized in Figure A.II-20, a and b, which shows the relationship between the incidence of lung cancer and radiation dose for inhaled soluble transuranics and inhaled insoluble plutonium dioxide, respectively. If the slope estimates are taken as the best available, then the risk of lung cancer for rats that inhaled soluble transuranics was about 8×10^{-4} cases per rad, while for rats that inhaled relatively insoluble PuO_2 the risk was about 16×10^{-4}. Therefore, the risk to rats from insoluble plutonium was about double that from soluble alpha-emitters. Although the difference is statistically significant, the authors cautioned that "because of the biological problems characteristic of these kinds of experiments, the quality of the data and evidence of nonlinearity, the statistical power of such a test is questionable."

An analysis of experimental animal data for induction of lung cancer by external irradiation and by internally deposited alpha and beta-gamma-emitters has been recently completed [66]. Lung cancer effectiveness factors were calculated for each type of radiation exposure. Values of the ratio of effectiveness of alpha irradiation compared with uniform irradiation ranged from 0.35 to 110 with a geometric mean of 4. For alpha-irradiation, compared with beta irradiation, values ranged from 0.06 to 25 with a geometric mean of 2.5. The wide range of values resulted from the large variability of the data. While alpha irradiation was generally more effective than uniform irradiation and beta irradiation, for all dose levels and all animal species the mean differences were less than 10, the value usually taken as the quality factor for alpha irradiation.

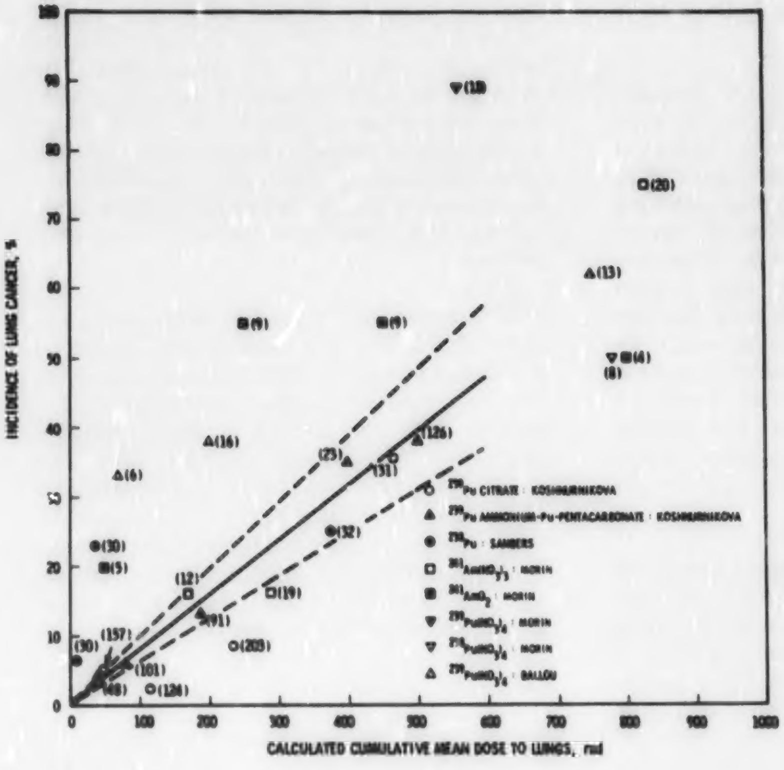

FIGURE A.II-20a

Incidence of Lung Cancer in Rats after Inhalation of Soluble Alpha-Emitting Radionuclides [67] (The number of animals in each group is given in parentheses)

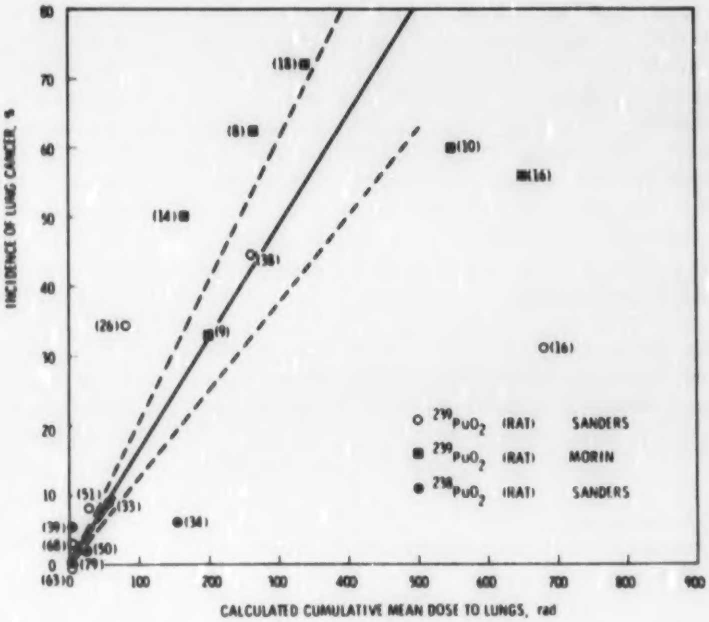

FIGURE A.II-20b

Incidence of Lung Cancer after Inhalation of Insoluble Alpha-Emitting Radionuclides [67]. (The number of animals in each group is given in parentheses)

Analysis of Lung Tumor Mortality in the Battelle Beagle Lifespan Experiment*

Forty beagles in the Battelle group between 12 and 43 months of age (mean age = 562 days) were given "single, 10-30 minute inhalation exposures to $^{239}PuO_2$ aerosols via a mask" [52]. Eighteen of the original 40 dogs died with lung tumors as the primary cause of death. Seventeen died of other causes, primarily pulmonary fibrosis, and in nine of these lung tumors were in evidence even though they had not developed to the point of causing death. Finally, five dogs were sacrificed for analysis of tissue distribution of plutonium. Sacrificed animals were asymptomatic for lung tumors and none had lung tumors at autopsy. Details of the experimental procedures and results are given by Park et al. [52].

In order to use the Battelle beagle experiment to test the Cochran and Tamplin Hot Particle Hypothesis it is necessary to assess the lung tumor mortality rate in these beagles in relation to the estimated number of hot particles deposited in their lungs. It must first be noted that the Cochran and Tamplin risk factor of 1/2000 per hot particle is a risk of death from lung cancer. Thus, Cochran and Tamplin used cancer death risks given in the BEIR report [68] to calculate their estimate that 1/1000 is the lung cancer death risk which would result from continuous lung exposure at the current maximum permissible level for workers. Since they went on to calculate that such a risk would be generated by two hot particles with a risk of 1/2000 each, it is clear that the latter figure is a risk of death from lung cancer, as opposed to a risk, for example, that an individual will have an incipient lung cancer developing.

For the purposes of the present analysis, the risk of beagles in the Battelle study dying from lung cancer will be assessed for a risk period extending from the time of the initial exposure to the aerosol to 3600 days thereafter. At the end of the risk period the animals would be expected to have averaged 11.5 years of age, since the average animal was 562 days of age at the time of initial exposure. Although the mean life span is not known accurately for the normal unirradiated beagle in the Battelle colony, 11.5 years is probably a reasonable estimate.

Two methods will be used to derive the accumulated risk of death from a lung cancer in the Battelle group at 3600 days postinhalation. The first method involves construction of a survival table and analysis of the cumulative proportion of survivors at 3600 days. The results are shown in Table A.II-17. Without any assumptions about the nature of the cancer induction process, the estimated cumulative probability of dying from lung cancer, Q_x, at x days after inhalation of the aerosol can be derived from the relationship:

$$Q_x = 1 - P_x \qquad (1)$$

where P_x is the cumulative probability of surviving x days after inhalation of the aerosol.

It is evident from Table A.II-17 that for the animal that died of lung cancer at 3537 days postinhalation, the probability of dying from lung cancer was high enough, 0.82 (1-0.178), to make it likely that the animal could have had more than one primary lethal lung cancer. A lethal lung cancer is defined as one that has developed to the point at which it is capable of causing the animal's death.

The probability of dying from lung cancer is more strictly the probability of dying from at least one lethal lung cancer. Since cancers are expected to arise as rare independent events it is appropriate to use the Poisson distribution to estimate the frequency of multiple primary cancers. It should be noted that the actual number of primary cancers cannot be directly observed since multiple cancer foci may result either from metastases of a single primary cancer or from multiple primary cancers.

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*Prepared for the Committee's use by E. B. Lewis

TABLE A.II-17

Survival Table for the Battelle Group of Beagles

(1) x Time in days after inhalation of $^{239}PuO_2$	(2) n_x No. of dogs alive at the start of the day, x	(3) d_x No. of dogs dying of lung cancer during the day, x	(4) P_x Cumulative probability of survival at the end of day, x	(5) m_x (a) Calculated mean number of lethal lung cancers per dog alive at end of day, x
1629	24	1	0.958	0.043
1635	23	1	0.917	0.087
1823	20	1	0.871	0.138
2211	16	1	0.816	0.203
2229	15	1	0.762	0.272
2341	14	1	0.708	0.346
2356	13	1	0.653	0.426
2412	11	1	0.594	0.521
2565	10	1	0.534	0.627
2792	9	1	0.475	0.744
2809	8	1	0.416	0.878
3079	7	1	0.356	1.032
3313	6	1	0.297	1.214
3441	5	1	0.238	1.438
3537	4	1	0.178	1.725
3664	3	1	0.119	2.131
3676	2	1	0.059	2.824
4068	1	1	0.000	—

(a) $m_x = (-) \log_e (P_x)$

The probability of surviving to x days without a lung cancer is given by the first term of the Poisson distribution, e^{-m} or [exp (-m)], where m is the mean number of lethal lung cancers that the average animal in the population would possess at x days. It follows that the cumulative probability of dying from at least one lung cancer at x days is

$$Q_x = 1 - [\exp(-m_x)] \qquad (2)$$

Combining Equations 1 and 2 gives

$$m_x = (-) \log_e (P_x) \qquad (3)$$

Values of m calculated in this way are shown in column 5 of Table A.II-17. For the animal that died at 3537 days postinhalation the value of m is 1.7. The next death occurred at 3664 days, for which time the corresponding value of m is 2.1 cancers. At 3600 days, therefore, the average number of lethal cancers per animal would have been approximately two.

For the purpose of making comparative risk evaluations, it becomes essential to determine also the rate at which the beagles died of lung cancers as a function of the duration of risk; that is, the elapsed time, t, since the initial day of exposure to the radioactive aerosol. For this purpose a life table method of analysis was chosen, since this method has considerable power to dissect the time course of tumor development even when, as in the present case, there are relatively small numbers of animals at risk [69]. The probability of a beagle in the Battelle group dying from lung cancer, q_x, in a given interval (arbitrarily, 100 days in length) is found to be adequately expressed in terms of a simple power function of t, namely:

$$q_x = a\,(t)^b \qquad (4)$$

where a and b are constants. Actually the analysis has been carried out using the more precise relationship,

$$q_x = 1 - \exp[-a\,(t)^b] \qquad (5)$$

where the quantity, $a\,(t)^b$, is equivalent to m_x of Equation 2 and can be thought of as a rate, R_m, at which lethal lung cancers develop in a given interval. For a sufficiently small interval, q_x will in fact be equivalent to R_m for all practical purposes, and in the present case it turns out that a choice of an interval of 100 days in length satisfies this condition. By analogy with Equation 2, Equation 5 allows for the contingency that no matter how small the interval in the life table there is a finite chance that more than one lethal lung cancer will develop in that interval.

Briefly, the method of fitting the constants involved use of a computer to generate a life table for each pair of values of a and b to be tested and then to test goodness of fit between observed and expected numbers of lung cancer deaths by the Chi-squared criterion, first grouping such numbers into six successive 800-day intervals. In this way the values of a and b that result in a minimum value of Chi-squared are found to be 9.0×10^{-15} and 3.2, respectively, for t expressed in days. The life table based on these values is shown in Table A.II-18 and the resultant Chi-squared value is 3.8, which for three degrees of freedom is not statistically significant (P = 0.3). Even when a finer grouping into 400-day intervals is used, in none of the 12 intervals does the difference between observed and expected numbers of deaths give cause for concern. If Equation 4 is used instead of Equation 5, identical results, including identical values of a and b, are obtained. Substitution of these values of a and b in the right hand side of Equation 4 and integration over the limits of 0 to 3600 days gives 1.9 for the mean number of lethal lung cancers per animal at 3600 days after exposure to the aerosol, which is in good agreement with the number calculated from the survival table (Table A.II-17); namely, two, as shown above.

An approximate upper limit for the mean number of lethal lung cancers at 3600 days postinhalation has been derived by first estimating an upper limit for the constant b. When b is as high as 4.5, Chi-squared is at a

TABLE A. II-18

Life-Table Analysis of Lung Tumor Mortality in the Battelle Group of Beagle Dogs

(1) $\bar{x}$ Mid-point in days of each successive 100-day interval beginning on the day of exposure to $^{239}PuO_2$	(2) l_x No. of dogs alive at the start of interval	(3) w_x No. of dogs dead due to cause other than cancer (No. of dogs with lung cancer which was not the primary cause of death)	(4) s_x No. of dogs sacrificed	(5) d_x No. of dogs dead with primary lung cancer during interval	(6) $[d_x]$ Expected no. of dogs dead with lung cancer[a] $[dx] = [l'_x] [q_x]$ during interval	(7) $[l_x]$ Expected no. of dogs alive at the start of interval[b]	(8) $[l'_x]$ No. of dogs at risk of dying of lung cancer during interval[c]	(9) $[q_x]$ Probability that dog will die of at least one lung cancer during interval[d]	(10) d_x Observed no. of dogs dead with primary lung cancer in 400 day interval	(11) $[d_x]$ Expected no. of dogs dead with lung cancer in 400 day interval
50	40	0	0	0	0.00+	40	40	0.00+	0	0.0+
150	40	0	0	0	0.00+	40.0-	40.0-	0.00+		
250	40	0	0	0	0.00+	40.0-	40.0-	0.00+		
350	40	0	0	0	0.00+	40.0-	40.0-	0.00+		
450	40	0	0	0	0.01	40.0-	40.0-	0.00+	0	0.1
550	40	0	0	0	0.02	40.0-	40.0-	0.00+		
650	40	0	0	0	0.04	40.0-	40.0-	0.00+		
750	40	0	0	0	0.06	40.0-	40.0-	0.00+		
850	40	1	3	0	0.08	39.9	37.9	0.00	0	0.5
950	36	2	0	0	0.11	35.8	34.8	0.00		
1050	34	0	0	0	0.14	33.7	33.7	0.00		
1150	34	2 (2)	0	0	0.18	33.5	32.5	0.01		
1250	32	1	0	0	0.22	31.4	30.9	0.01	0	1.1
1350	31	3 (2)	1	0	0.26	30.1	28.1	0.01		
1450	27	1	0	0	0.30	25.9	25.4	0.01		
1550	26	1	0	0	0.35	24.6	24.1	0.01		
1650	25	1 (1)	1	2	0.39	23.2	22.2	0.02	3	1.9
1750	21	1 (1)	0	0	0.43	20.8	20.3	0.02		
1850	20	0	0	1	0.49	19.4	19.4	0.03		
1950	19	0	0	0	0.57	18.9	18.9	0.03		
2050	19	3 (2)	0	0	0.59	18.3	16.8	0.04	4	2.6
2150	16	0	0	0	0.60	14.8	14.8	0.04		
2250	16	0	0	2	0.66	14.2	14.2	0.05		
2350	14	1 (1)	0	2	0.70	13.5	13.0	0.05		
2450	11	0	0	1	0.72	12.3	11.8	0.06	3	3.1
2550	10	0	0	1	0.77	11.1	11.1	0.07		
2650	9	0	0	0	0.80	10.3	10.3	0.08		
2750	9	0	0	1	0.83	9.5	9.5	0.09		
2850	8	0	0	1	0.84	8.7	8.7	0.10	2	3.3
2950	7	0	0	0	0.85	7.8	7.8	0.11		
3050	7	0	0	1	0.83	7.0	7.0	0.12		
3150	6	0	0	0	0.81	6.2	6.2	0.13		
3250	6	0	0	0	0.77	5.3	5.3	0.14	3	2.8
3350	6	0	0	1	0.72	4.6	4.6	0.16		
3450	5	0	0	1	0.66	3.9	3.9	0.17		
3550	4	0	0	1	0.60	3.2	3.2	0.19		

TABLE A.II-18 (Continued)

(1) T Mid-point in days of each successive 100-day interval beginning on the day of exposure to $^{239}PuO_2$	(2) l_x No. of dogs alive at the start of interval	(3) w_x No. of dogs dead due to cause other than cancer. (No. of dogs with lung cancer which was not the primary cause of death.)	(4) s_x No. of dogs sacrificed	(5) d_x No. of dogs dead with primary lung cancer during interval	(6) $[d_x]$ Expected no. of dogs dead with lung cancer[a] $[d_x] = [l'_x][q_x]$ during interval	(7) $[l_x]$ Expected no. of dogs alive at the start of interval [b]	(8) $[l'_x]$ No. of dogs at risk of dying of lung cancer during interval [c]	(9) $[q_x]$ Probability that dog will die of at least one lung cancer during interval. [d]	(10) d_x Observed no. of dogs dead with primary lung cancer in 400 day interval	(11) $[d_x]$ Expected no. of dogs dead with lung cancer in 400 day interval
3650	3	0	0	2	0.52	2.6	2.6	0.20	2	1.7
3750	1	0	0	0	0.45	2.1	2.1	0.22		
3850	1	0	0	0	0.38	1.6	1.6	0.23		
3950	1	0	0	0	0.31	1.2	1.2	0.25		
4050	1	0	0	1	0.25	0.9	0.9	0.27	1	0.7
4150	0	0	0	0	0.20	0.7	0.7	0.29		
4250	0	0	0	0	0.15	0.5	0.5	0.31		
4350	0	0	0	0	0.11	0.3	0.3	0.33		
4450+[e]	0	0	0	0	0.22	0.2	.....	.....	0	0.2
Total	...	17 (9)	5	18	17.99	.....	.....	.....	18	18.0

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[a] Based on model described in text.

[b] Computed by subtracting from the value of $[l_x]$ at the start of the previous interval, the sum of the values of $[d_x]$, w_x and s_x derived from the previous interval.

[c] The quantity $[l'_x]$ for a given interval is approximated by subtracting from the value of $[l_x]$ for that interval one-half the sum of the values of w_x and s_x for that interval.

[d] Derived from expression, $1-e^{-m}$ where m, the mean number of lethal tumors per animal, is evaluated from the empirically determined expression, $m = 9 \times 10^{-45} (t)^{3.2}$. Values of $[q_x]$ are rounded to two decimal places.

[e] The last of the 40 dogs died at 4068 days post-exposure; however, the table is extended to show the number of expected deaths during subsequent 400-day intervals until at 4400 days the total of all expected numbers thereafter is combined and is 0.2 death as shown in columns 6 and 11.

minimum when $a = 3.2 \times 10^{-19}$ but the corresponding value of P has dropped to 0.1; owing to the small numbers involved, such a procedure can only provide a rough estimate of 4.5 as the upper 90% confidence limit for b. When these latter values of a and b are substituted in Equation 4, integration over the limits of 0 to 3600 days gives a value of 2.1 tumors. In a similar way an upper limit for the constant a, when b is 3.2, is found to be 1.3×10^{-14}, which yields an estimate of 2.7 lethal lung cancers at 3600 days. By analogous methods a lower limit for the mean number of lethal lung cancers per animal at that time is 1.2.

If the age of the animal is substituted for t in Equation 4 by adding the mean age of the animals at the time of exposure to the aerosol (namely, 562 days), then the best fitting power of the age is found to be 4.0. The purpose of introducing age, as opposed to duration of risk, is solely to permit comparison of these results with the behavior of other cancer rates. Thus, the natural incidence rates of many types of cancers [70], including lung cancers [71], have been shown to vary also in accord with a power of the age of 4.0 or more. Doll [72] has also shown that radiation-induced leukemia rates in spondylitic patients increased steeply as age at time of irradiation increased and in a manner paralleling the increase in natural leukemia incidence rates with age. It is concluded that, in the case of lung cancer induced by alpha radiation, risk evaluation probably should be based upon the relative risk rather than the absolute risk method. This will be discussed more fully below.

The significance of the beagle findings will be assessed first in relation to the Hot Particle Hypothesis and then in relation to the problem of estimating radiation-induced lung cancer risks in human population groups. It is instructive to use the beagle experience to derive an upper limit for the lung cancer death risk per hot particle and then to compare that risk with the one Cochran and Tamplin derived from skin tumor data in rats. The estimate based on the beagle experience is an upper limit, in the sense that it is based on the arbitrary assumption that the average of two lethal lung cancers per animal at 3600 days postinhalation results entirely from a hot particle effect. For the animals that died of lung cancer before that time, the mean initial lung burden was 1.07 μCi. As shown in Table A.II-19, the average animal with such a burden is likely to have had deposited in its deep lungs at least 1.3 million Type 1 particles or at least 200,000 Type 2. (Type 1 and Type 2 refer to particles defined by Cochran and Tamplin as having specific activities of 0.07 pCi and 0.6 pCi, respectively.)

It follows that if the beagle experience is used to derive an estimate of the accumulated lung cancer death risk associated with any hot particle effect, then the upper limit for such a risk per Type 1 hot particle is roughly 1.5 per million (2 lethal lung cancers/1,300,000 particles), or one per 100,000 (2/200,000) per Type 2 particle. These hypothetical risks could be one or more orders of magnitude lower, if not zero, if the bulk of the lung cancer risk experienced by the beagles resulted from the generalized alpha irradiation from the total ^{239}Pu activity in their lungs. These risk estimates based on the beagle experience are thus strikingly lower than the risk of one per 2,000 per hot particle of either Type 1 or Type 2 which Cochran and Tamplin derived on the basis of their analysis of data on skin tumors in rats.

It is especially instructive to assess the induced lung cancer risks experienced by the Battelle beagle group in relation to estimates of lung cancer risks in human beings based upon the experience of occupational groups exposed to alpha radiation. At the outset it should be noted that the BEIR Committee suggested the use of two methods of assessing cancer death risks, including those from lung cancer; namely, an absolute risk and a relative risk method. There were insufficient data to decide between the two methods and the committee therefore calculated risks by both methods.

The BEIR Committee suggested that if the absolute risk method is adopted a risk constant of one lung cancer death per million person-years per rem should be used, this constant

TABLE A.II-19

Estimated Number of Hot Particles Deposited in the Pulmonary Regions of the Battelle Group of 15 Beagles That Died Between 0 and 3600 Days of Lung Cancer. [Calculated on the assumption of (1) a log normal frequency distribution with respect to particle size before inhalation of the aerosol; and (2) a constant deposition frequency in the pulmonary regions; that is, any particle is equally likely to reach the pulmonary regions regardless of its size.]

	Type of Aerosol		
	A CMD[b] = 0.5 μm σ_g [c] = 2.3	B CMD = 0.25 μm σ_g = 2.1	Weighted Means
Number of Dogs Exposed That Died of Lung Cancer	5	10	
Mean Initial Lung Burden (ILB), μCi	1.01	1.10[a]	1.07
Estimated Number of Type 1 Hot Particles ($\geq$0.07 pCi)	4.1 x 10^5	1.8 x 10^6	1.3 x 10^6
Estimated Number of Type 2 Hot Particles ($\geq$0.6 pCi)	1.4 x 10^5	2.1 x 10^5	1.9 x 10^5

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[a] For one of the dogs exposed to aerosol "B" the initial lung burden has not been determined. Therefore, the initial lung burdens and particle number estimates are based upon 10 instead of 11 dogs; the omitted dog died with a lung cancer as cause of death 3537 days after exposure to the aerosol.

[b] CMD = Count Median Diameter

[c] σ_g = Geometric Standard Deviation

NOTE: When allowance is made for differential pulmonary deposition (see Figure A.II-2), the numbers of Type 1 and Type 2 particles deposited in the deep lungs are likely to have been higher than those shown in this table.

to take effect after a 15-year latent period and to remain in effect for either (a) a 30-year period or (b) indefinitely. An estimate can then readily be derived for the accumulated lung cancer risk a person might be expected to acquire by age 70, for example, if he had been continuously exposed over his working life to the maximum permissible occupational level as currently set (15 rem per year to the lung). The accumulated dose over a 48-year work span extending from age 18 to 65 inclusive amounts to 720 rem (48 x 15) and the duration over which the risk constant is assumed to apply is either (a) 30 years or (b) 36 years (from age 34, after a 15-year latent period, to the start of age 70). For present purposes the more conservative assumption (b) is desired. The resultant accumulated lung cancer death risk is 0.026 (1 x 10^{-6} x 720 x 36). (Strictly speaking, for chronic exposures at a constant dose rate the effective dose is one-half of the total accumulated dose, as shown by Marinelli [73]; however, since the risk constant used in the BEIR Report was derived on the basis of the accumulated rather than the effective dose, it is necessary to use the accumulated dose in applying that risk constant.)

The BEIR Committee suggested that if the relative risk method is used, a value of 0.29% should be adopted for the incremental relative risk per rem. For present purposes, before the relative risk constant can be applied it is necessary to estimate the accumulated lung cancer death risk by age 70 for adult males in the general population. That is, such males constitute the population from which the occupational groups under consideration are expected to be largely drawn; namely, groups that mine or process heavy alpha-emitting elements. From age-specific death rates that have been averaged over the years 1962-1967 and tabulated by Burbank [74], the accumulated lung cancer death risk by age 70 can be estimated from the cumulative proportion of survivors at that age and is found to be 0.036. Such an estimate must be used with caution since it is known that it is markedly influenced by such factors as the smoking habits which characterized different age groups in the population at risk. With this reservation in mind, the accumulated lung cancer death risk at age 70 can be estimated as 0.075 (0.036 x 720 x 0.0029) for the hypothetical case of continuous occupational exposure of the lungs at the maximum permissible level. It should be emphasized that in applying the relative risk as well as the absolute risk method the underlying assumption is that of a linear dose-response relationship over the range of exposures being considered. (Again it should be stressed that since the BEIR Committee used the cumulative dose, as opposed to the effective mean dose, to derive the relative risk constant in the case of chronic exposures, it obviously is necessary when applying their estimate of that constant to use the cumulative dose experienced by the population under consideration.)

To recapitulate, 0.026 and 0.075 are estimates based on absolute risk and relative risk methods, respectively, of the accumulated death risk from lung cancer by age 70 for the case of continuous occupational exposure of the lungs at 15 rem per year. As already indicated, the steepness with which lung cancer death rates in the Battelle beagles rose as a function of age strongly suggests that the relative risk estimate is the appropriate one to use in the present context of assessing lung cancer risk from alpha emitters.

The relative risk of 0.075, calculated for humans, will be used as a basis for testing whether the generalized alpha radiation to which the beagle's lungs were exposed can account for the observed lung cancer mortality in those animals. The effective lung dose of alpha radiation which the beagles had accumulated by 3600 days postinhalation amounted to approximately 51 times* the corresponding dose accumulated by age 70 in the hypothetical case of a worker exposed continuously at the occupational maximum permissible level (that is, the dose upon which the estimate of 0.075 is based). Hence on the basis of linear extrapolation (0.075 x 51) there should have been an average of 3.8 lethal lung cancers per animal at 3600 days compared to the two previously calculated tumors per animal estimated by the life table method. Since the relative risk constant is itself subject to considerable uncertainty, being based on sets of data for which the calculated values of that constant ranged from 0.0016 and 0.0068 [68], it can be inferred that the expected number of lethal lung cancers for the case of exposure of the human lung could have ranged from 2 to 9. For present purposes it suffices to note that the beagle lung cancer death risk is not markedly different from, and may have been less than, that which would be calculated on the basis of averaging alpha radiation doses over the entire lung.

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*The mean initial lung burden of the 15 animals that died of lung cancer between 0 and 3600 days postinhalation was 1.07 μCi, which corresponds to an initial dose rate of 2.05 rad per day. The effective half-life of this activity in the lungs of these beagles averaged 970 days. The total accumulated lung dose at 3600 days is found to be 2575 rad, or 25,750 rem if a quality factor of 10 is used for converting rad of alpha radiation to rem. Marinelli [73] has shown that, in determining a linear dose-response relationship, the effective dose is given by the mean accumulated dose, which in the present case is found to be 18,410 rem. For occupational exposure at 15 rem per year for 48 years the total accumulated dose to the lungs is 720 rem, which corresponds to a mean accumulated dose of 360 rem. Hence the ratio of the effective dose to the lungs of the Battelle beagles that died of lung cancer and the effective dose to human lungs from occupational exposure at the maximum permissible level is 51 (18,410/360).

Finally, it may be of interest to analyze Cochran and Tamplin's original statement that the maximum permissible lung burden (MPLB) should be reduced by a factor of 115,000. This factor, it will be recalled, was derived by dividing the maximum permissible lung burden of ^{239}Pu required to give a dose rate of 15 rem per year (0.016 μCi) by the total activity contained in two of their Type 1 hot particles (0.14 pCi). Their choice of two particles, as already noted, was based on two assumptions: 1) that the lung cancer death risk associated with continuous lung exposure at the rate of 15 rem per year was 1/1,000, and 2) that the lung cancer death risk per hot particle was 1/2,000. The present analysis indicates that the appropriate value for the first of these risks is 1/13 (0.075), rather than 1/1,000; while the value for the second risk is not 1/2,000 but instead has an upper limit of 1.5/1,000,000 per Type 1 and 1/100,000 per Type 2 hot particle. It follows that at least 50,000 Type 1 particles would be required to give the predicted lung cancer death risk of 0.075. That number of particles would constitute a total activity of 0.004 μCi or more and therefore would represent a factor of no less than 1/5, rather than one of 1/115,000, of the maximum permissible occupational level. Nor is the problem changed appreciably with the more recently defined Type 2 particle, since at least 7,500 of such particles would be required, corresponding to a total activity of 0.005 μCi or a factor of no less than 1/4, not 1/115,000. Since all of the lung cancer deaths in the Battelle group of beagles can be accounted for on the basis of the generalized alpha radiation, the actual risks associated with any hot particle effect may be so low as to be negligible when compared to the risk from the generalized alpha radiation.

Radiation standards, as currently applied, are not tied directly to any particular method of calculating risks but instead are set in terms of various absorbed dose levels to the whole body or to critical organs, depending upon the type of population group exposed. In relating such levels to risks, it is appropriate to use the methods outlined in the BEIR Report. Indeed, the relative risk method in the present case may be expected to predict adequately not only lung cancer risks from generalized alpha radiation but also those from insoluble particulates.

Summary

An analysis of lung cancer mortality rates in the Battelle group of beagles indicates that (1) the generalized alpha radiation from the total ^{239}Pu activity in their lungs is sufficient to account for all of the lung cancer deaths which occurred in these animals, and (2) if there is a hot particle effect of the type postulated by Cochran and Tamplin, the risk of a lung cancer death per particle when calculated on the basis of the beagle experience is orders of magnitude smaller than they estimated and could well be so small that the contribution from any hot particle effect to the total lung cancer mortality is negligible. The beagle results also indicate that the relative risk method of assessing risks, as opposed to the absolute risk method, is likely to be the appropriate one for estimating lung cancer risks in human populations exposed to radiation.

Human Beings*

Lung cancer is the common designation for a number of types of cancer arising in the respiratory tract. By far the most frequent type in man is cancer arising from bronchial epithelial cells in the first few branches of the bronchial tree. On histological grounds, these bronchial tumors are divided into epidermoid cancers, small and large cell undifferentiated cancers, adenocarcinomas, and mixed types. There are also rare tumors, carcinoids, that arise from argentaffin cells in the bronchial wall.

There remains a controversy about the origin cells of the epidermoid and undifferentiated cancers and adenocarcinomas. Most authors believe that these all derive from epithelial stem cells, with the final histological type depending on the degree of differentiation achieved by the cell line that makes up the tumor [75]. Regardless of whether these cancer cells have different parent cells, the important point is that all three types are increased in those exposed to certain environmental agents, such as cigarette smokers [76,77] or persons occupationally exposed to carcinogens [78]. Smokers have an especially large increase in epidermoid cancers while undifferentiated cancers usually predominate among persons who develop bronchial cancers from occupational exposures.

Tumors also arise from alveolar cells [79] and cells in the bronchiolo-alveolar region. Some authors have concluded that the bronchiolo-alveolar tumors arise from terminal bronchial cells such as the Clara or the argentaffin cells [80]. These are rare cancers in man [81] and, unlike the bronchial epithelial cancers, have not been found to be increased in smokers or in groups exposed to environmental carcinogens. Thus they constitute a higher proportion of tumors in nonsmokers than in smokers, but they represent at present no more than a few percent of all lung cancers observed in the population at large.

Finally, there are cancers derived from plural elements such as the mesotheliomas. Recent work has shown that these rare tumors are nearly always associated with exposure to asbestos. In addition, and very rarely in the lung tissues, tumors may occur from connective tissues or other cell types, such as fibrosarcomas, leiomyomas, and angiosarcomas. These tumors are not now known to be related to environmental exposures to carcinogens.

The number of agents known to induce human bronchial cancers continues to grow. With the past few years, evidence has been obtained that occupational inhalation of bis-chloromethyl ether, nickel compounds and arsenic compound is associated with increased risk of bronchial cancer. Bis-chloromethyl ether, an extremely potent carcinogen in experimental animals, leads especially to small cell undifferentiated bronchial cancers in man. Thus, these agents join exposure to ionizing radiation, asbestos, mustard gas, chromate dust and, of course, cigarette smoke as environmental agents capable of causing bronchial cancer, now the most common cause of cancer in males in the United States.

Sensitivity of Lung Tissue Cells to Induction of Cancer by Environmental Agents, Including Ionizing Radiation

Exposure of lung tissues to most of the numerous chemical and physical agents associated with increased lung cancer risk has been by inhalation; an exception, discussed below, is exposure to ionizing radiation experienced by the Hiroshima survivors and patients who received x-ray treatment for *ankylosing spondylitis*. The exposure dose of the gases (e.g., mustard gas or bis-chloromethyl ether) to various tissues of the lungs will depend on their water solubility (highly soluble gases will be removed in the upper respiratory tract) and the surface area of the tissues exposed (since diffusion governs uptake). Mustard gas is sparingly soluble in water and thus its uptake is determined by the surface area. Similar considerations apply to the poorly-soluble respirable dusts such as arsenic trioxide and chromates. In the particle size range which can reach the lungs and tracheobronchial tree, diffusion also governs most of the deposition process. This means that, on inhalation, initial deposition of these materials occurs predominantly in the alveoli of the lung, rather than in the ciliated bronchial region, because of the very much larger surface area of the alveoli (more than 100 times greater).

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*Prepared for the Committee's use by E. P. Radford

The important datum, however, is the dose delivered to cells. Since the cells of the alveolar surface are much more attenuated than those of the ciliated epithelium, if deposition of a carcinogen is proportional to the gas-liquid surface area then obviously the alveolar cells will receive a larger dose of a diffusing agent than the bronchial epithelial cells. On the basis of this reasoning, therefore, if the sensitivity to cancerous transformation of the epithelial cells of the respiratory tract is equal throughout, then the cells of the alveoli, especially the type I cells (since they receive the highest dose of these agents) should give rise to many more cancers than the bronchial epithelium. This reasoning applies equally to cigarette smoke. In fact, there is no evidence that alveolar or bronchocell cancers are associated with inhalation of these carcinogenic gases, submicron dusts, or cigarette smoke. Although the groups exposed to occupational carcinogens have been relatively small, if alveolar or bronchiolo-alveolar cancers had increased they would have been immeddiately detected because these cancers are so rare in the general population. (Pleural and peritoneal mesotheliomas, the first type of cancer shown conclusively to be related to asbestos exposure, were noted precisely because they are so rare and thus the increase observed in workers handling asbestos was especially striking.)

This report, of course, is concerned with the hazard from inhaled apha-emitting elements. We have extensive evidence, both for cancer risk and site of cancer origin, in one human group exposed to alpha-emitters, underground uranium miners. Data on origin and cell type of the cancers are especially complete for the U.S. uranium miners studied by Saccomanno and his associates [77]. Before considering this group in some detail, however, it is worthwhile to review the lung cancer experience in populations exposed to external radiation.

In British studies of patients treated with x-rays for *ankylosing spondylitis* [82] the x-ray was directed principally at the thoracic and lumbar spine. From analysis of the dose to the lung tissues, it is reasonable to conclude that much of the lung parenchyma received the same x-ray dose as did the bronchial tissues. In the Hiroshima survivors who were exposed to both neutrons and penetrating gamma radiation, the neutron dose to the bronchial tissues, because of shielding effects, would have been somewhat lower than to the alveolar tissues closest to the direction of the bomb. In both groups, with well over 100 excess cancers observed, there is only a slight indication of an increase in alveolar cancers [83].

The U.S. uranium miner study offers the best quantitative evidence of the relative sensitivities of different lung tissues to alpha irradiation [84]. These miners are exposed to radiation from the daughters of radon; the half-lives of these daughters are short, up to 30 minutes, and most of them are inhaled on respirable dust particles in the submicron size range. These particles are deposited in the respiratory tract, where movement is primarily by diffusion. The time period during which they move about in the respiratory tract is limited by their physical decay rate. Calculation of the alpha dose to bronchial epithelium and lung tissue is complex but Albert estimates that the number of alpha emissions in the alveoli from inhalation of a typical mine atmosphere is approximately 10 times higher than that released in the bronchial tree in the regions where tumors form.

Saccomanno has examined histologically the lung tissues of approximately 200 lung cancer cases among these miners and reports that only one bronchiolo-alveolar cancer has been observed. Considering the population at risk, this is somewhat less than might be expected on the basis of the frequency of these cancers in the male population but, even if we accept this case as a radiogenic cancer, it would appear that the radiosensitivity of the bronchial epithelium in man is at least 100 times that of the alveolar or bronchiolo-alveolar tissues. In fact, the relative sensitivity may be much greater.

For alpha irradiation therefore, as well as for exposure to dusts and chemical agents in man, alveolar and bronchiolo-alveolar tissues appear to be very much more resistant to cancer induction than the bronchial epithelial cells. This conclusion varies somewhat from experience with cancer induction in experimental animals (discussed in the previous section). Some possible explanations for the special sensitivity of the bronchial epithelium in man are: a) the bronchial epithelium is more rapidly renewed by cell division than are the alveolar epithelium or connective tissue elements and radiosensitivity is related to this quality; b) most (but not all) occupational bronchial cancers have been observed in cigarette smokers who had been exposed to irritants in smoke and many of whom had chronic bronchitis, both of which may make the epithelium more sensitive to carcinogens; c) human populations are commonly and repeatedly exposed to viral infections of the respiratory epithelium which cause rapid loss of epithelial cells, requiring rapid proliferation of stem cells to repopulate the mucosa. Moreover, these viruses could directly contribute to the process of transformation to a cancer; and d) other inhaled pollens, dusts, and gases in the general environment may contribute to bronchial irritation. Regardless of the reasons for this sensitivity, the tissue at special risk in man from inhaled transuranic elements is probably the bronchial epithelium, especially in the more proximal regions of the bronchial tree.

Dose-Response Data for Cancer Induction by Alpha Radiation Exposure in Man

An extensive review of dose-response data for cancer induction by alpha radiation was presented in the BEIR Report in 1972 [68]. The Committee's position as reflected in that document is summarized below, followed by an account of recent developments relevant to the issue of toxicity of alpha-emitters.

Dose-response data have been obtained from a number of underground mining groups exposed to relatively high levels of radon daughters in the past and to individuals exposed to thoron exhaled as a daughter from body burdens of thorium salts given for diagnostic purposes. The best data have been from the U.S. uranium miners [84] and the Newfoundland fluorspar miners [85]. From the analysis done in 1972, these two groups showed similar risk estimates per rem of exposure to the bronchial epithelium, although the fluorspar miners gave an estimate of 1.65 excess lung cancer cases/rem/10^6 person-years, while the figure for the uranium miners was 0.63 cases/rem/10^6 person-years. It was pointed out in the BEIR Report that all of these populations are still at increased lung cancer risk and, thus, these figures are likely to be revised upward. The similarity of risk estimates for lung cancer based on the gamma and neutron-irradiated Hiroshima survivors and the miners supported the conclusion that the radiosensitivity of the lung tissues was consistent with well-known radiobiological principles.

Documentation of new underground mining populations exposed to elevated radon daughter concentrations and an updating of the experience of the U.S. uranium miner group have contributed new evidence on the question of risk from alpha irradiation. The new mining populations that have been studied are in iron and zinc mines in Sweden [86,87]. The cumulative dose response data in these miners are comparable to those of the other groups but the most significant aspect of these mines is that the radon daughter concentrations were relatively low, with exposures in some cases below 1 Working Level. This evidence, therefore, extends our documentation of increased cancer risk to lower dose rates than had been observed previously in the uranium and fluorspar miners.

Finally, it has been possible to update the U.S. uranium miners study group to 1972 [88]. As expected, the cancer incidence rate has remained high, at roughly 30 times the rate in the remainder of the U.S. population. Adding the new lung cancer cases, modifying the definition of period at risk from 5 years after beginning of mining (used in the Interagency and BEIR Reports) to 10 years after beginning of mining, and eliminating three cases which occurred during the 5-10 year period (which is probably less time than the latent period for lung cancer) results in a revised absolute risk of about 2 cases/rem/10^6 person-years. The new data suggest that the straight-line fit of the dose-response curve used in the BEIR Report is in error, with the risk in the lower dose categories higher per rad than in the highest dose groups. Since the lowest dose category (<120 WLM) contains few cases and the statistical range of uncertainty is very large as a result, there is a corresponding uncertainty in the exact basis for calculating the risk in this group. It should be noted that these risk estimates may continue to increase if more cases occur, especially if with advancing age, relative risk compared to the general population remains high.

Comparison of Human and Animal Radiocarcinogen Effects*

While responses to "toxic" levels of external radiation and internal emitters in people and experimental animals have been studied over the past 75 years, uncertainties regarding the quantitation of effect and appropriate methods to scale dosage, time and effect (risk) still exist. Furthermore, human experience has been limited and usually has been observed through epidemiological, retrospective studies while laboratory studies on animals are prospective in nature. There is no radionuclide (or any other agent) for which toxic levels cannot be determined. The lungs in which the radionuclide is deposited do not appear to be uniquely sensitive or resistant to radiation-induced effects, including cancer, when compared to other comparably exposed tissues. However, despite intensive study, the exact mechanisms of radiation-induced cancer are still unknown. Many theories have been proposed, usually invoking a series of initiating and promoting factors for which some data are available, but it appears likely that no single model is universally acceptable [89].

In the absence of human data, the relationship between radiation dose and biological effects determined in animal experiments have been used to predict human consequences [90]. The most common parameters used have been the organ-averaged cumulative radiation dose and the crude excess incidence of effect (i.e., the number of animals manifesting the effect divided by the total number of dosed or dead animals at each exposure level). This statistic provides an estimate of fraction or percent effect per unit dose, but is fairly species (e.g., lifespan) dependent. While some long-lived animals, such as dogs and nonhuman primates, have been and are being studied, most of our animal data have been derived from relatively short-lived rodents [91,92].

A comparison of the interspecies radiobiology of inhaled alpha particles is hampered by the lack of direct human experience. Several indirect approaches can be used which attempt to "normalize" the spatial and temporal dose and metabolic and anatomic factors as well as differences in pathologic appearance, spontaneous disease and life expectancy. People are larger and live longer than experimental animals in the laboratory; however, there are probably fewer differences than similarities. The special case of lung cancer in people is somewhat obscured by problems relating to use of tobacco products and perhaps other occupational and environmental atmospheric pollutants. Table A.II-20 gives some quantitative interspecies comparisons.

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*Prepared for the Committee's use by M. Goldman

TABLE A.II-20

Some Species Intercomparisons

	Mice	Rats	Dogs	Human Beings
Life Span (yr)	3	4	13	72
Adult Mass (kg)	0.03	0.4	10	70
Lung Mass (g)	0.4	2	75	1000
Bone Mass (g)	3	40	1000	7000
Liver Mass (g)	4	10?	375	1700
Lymph Node (TB) Mass (g)	$\sim$0.1?	$\sim$1?	35	250
PuO_2 Lung Ret., $\bar{T}_b$ (da)	200- 500	250 550	300- 1000	240- 650

Conventional Approach

The interspecies comparison most used in risk assessments is time independent and attempts to use the linear dose to risk approach to calculate the absolute percent increase in effect per unit of dose [68,93]. For bronchial lung cancer, absolute estimates range from 0.6 (ABCC) to 1.61 (fluorspar miners) cases per yr/rem/10^6 persons, with an average of 1/10^6/yr/rem. Since the data are as yet incomplete, the risk may be twice as high in the final analysis (i.e., 2/10^6/yr/rem). If a 30 year "plateau" for risk obtains, the total excess yield might be 30 yr x 2/10^6/yr/rem or about 0.006%/rem; if a 50 year plateau obtains, the value could be about 0.01%/rem. Since all the radiation dose is not absorbed initially and there may be an effective latency per effective rem of about 20 years, it would appear that a reasonable estimate might be about 0.005%/rem.

Rodent inhalation studies with alpha-emitting radionuclide particles have yielded a variety of lung cancer risk estimates. Bair and Thomas [67] recently summarized many of these and derived a rodent lung cancer linear estimate of about 0.1%/rad. The single completed dog study at Battelle provides a crude upper limit of about 90%/1500 rads or 0.006%/rem which, although derived from very high doses, is not markedly different from the human and rodent estimates. In all three estimates, the lung dose is averaged over the entire lung volume and, as stated above, does not account for lifespan differences in survival rates at each dose level. Thus the classical approach suggests a rodent-dog-person risk of about 10^{-3} - 10^{-1}%/rem of lung irradiation.

The Radium-Bone Standard Approach

For many years the human experience with radium poisoning has been a benchmark for radionuclide standard-setting. Based primarily on studies of painters of watch dials, data on this bone-seeking alpha-emitting nuclide have been reviewed often and to date it would appear that doses in excess of several hundred (>700) rad of cumulative exposure have increased the risk for induction of skeletal tumors [94]. Furthermore, studies in rodents and dogs have attempted to simulate the human experience and provide a basis for further interspecies comparisons of the effects of alpha particles in mammals [95,96].

In addition, plutonium has also been administered to animals to provide data on plutonium in the skeleton [97,98]. One obvious comparison, therefore, would relate the effects of these two nuclides in one organ for different species. Jacobi [99] recently related the ^{226}Ra data for bone sarcomas in beagles and humans and attempted to account for temporal factors by use of an age-specific mortality rate for beagle bone cancer and an estimate of an induction period $\overline{\overline{T}}_i$ ($\overline{\overline{T}}_i = 2.0 + 5A^{-0.67}$; $\overline{\overline{T}}$ = years, A = µCi/kg injected). His dog-human comparison is shown in Figure A.II-21 and suggests a 5-10-fold lower risk to humans than to dogs at each mean alpha rad dose level.

Using a somewhat similar approach, Goldman et al. **[90]** compared mouse, dog, and man. Results are shown in Figure A.II-22.

Osteosarcomas in animals following injection of plutonium are summarized in Figure A.II-23 **[40]**. Except for the dog data (open circles), these data are derived from rodents. The dogs clearly are more responsive per rad than the rodents. An attempt to quantify the difference is shown in Figure A.II-24, which compares the plutonium in mice studies conducted by Finkel **[100]** at Argonne National Laboratory and the beagle plutonium study at Utah **[101]**. There is about a 30-fold difference between the two species over most of the range of plutonium injections, but only about a 2-fold difference for these two species for radium **[90]**. If one applies the distribution factor (DF) of 5 for plutonium relative to radium and uses, for example, the 10% risk (in rad) estimate for beagles and humans from Jacobi, a relationship such as the following can be derived.

$$\frac{\text{Ra dog bone}}{\text{Ra human bone}} \approx \frac{\text{Pu dog bone}}{\text{Pu human bone}}$$

$$\frac{440}{1500} \simeq \frac{440/5}{X}, X \simeq 300 \text{ rad/10\% plutonium bone tumors in man}$$

If linear, this would be an estimate of about 3 x 10^{-3}%/rem. To further extend the analogy of radium:plutonium, dog:man to estimate relation of lung cancers according to species requires assuming that both organs manifest the same ratio of sensitivity to tumor induction in each species. The comparison might be:

$$\frac{\text{Ra Dog}}{\text{Ra Man}} \text{(bone)} = \frac{\text{Pu Dog}}{\text{Pu Man}} \text{(lung)}$$

The 10% lung cancer incidence due to plutonium exposure in dogs is from the Battelle data of 90%/1500 rad. Thus the 10% yield

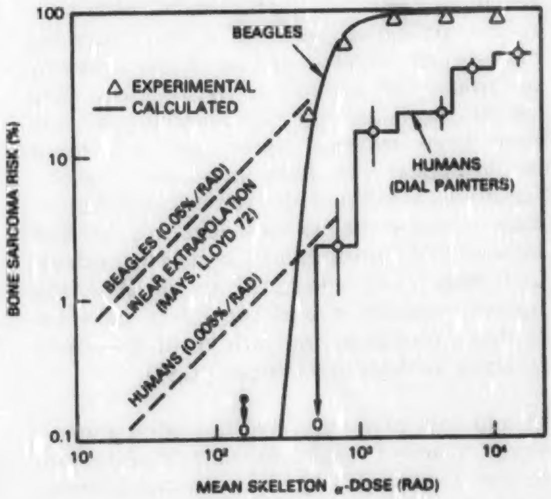

FIGURE A.II-21

Bone Sarcoma Incidence in Humans and Beagle Dogs from Exposure to ^{226}Ra **[99]**

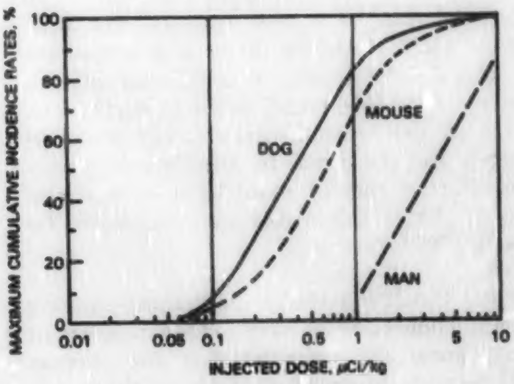

FIGURE A.II-22

Estimate of Incidence of Osteosarcomas in Man Based on Osteosarcoma Data Obtained from Mice and Dogs, Allowing for Differences in Radium Retention **[90]**

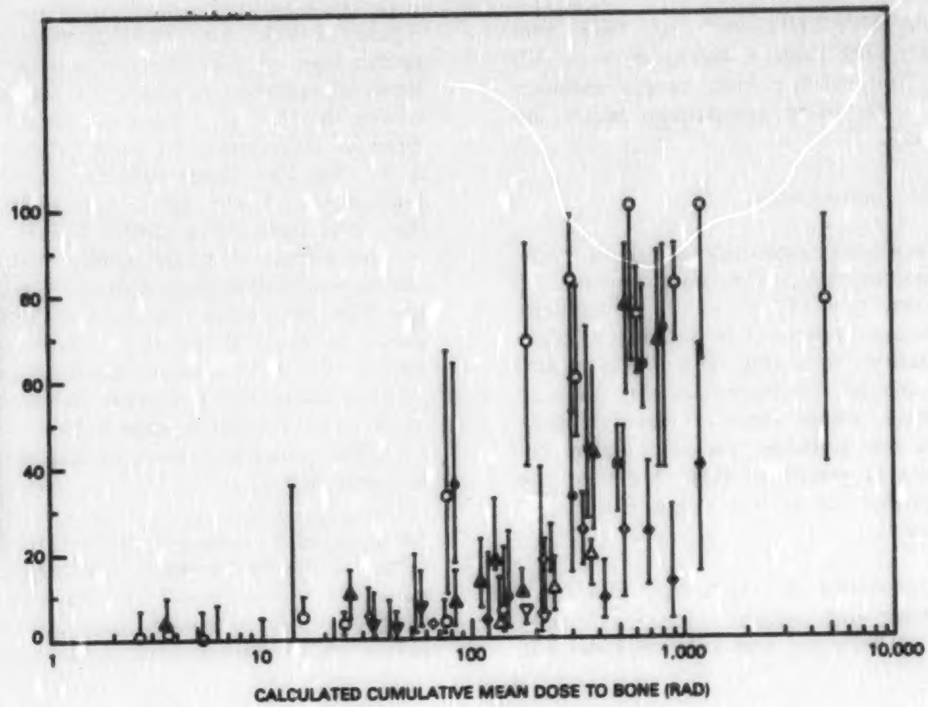

FIGURE A.II-23

Plutonium-Induced Osteosarcoma in Experimental Animals [40]

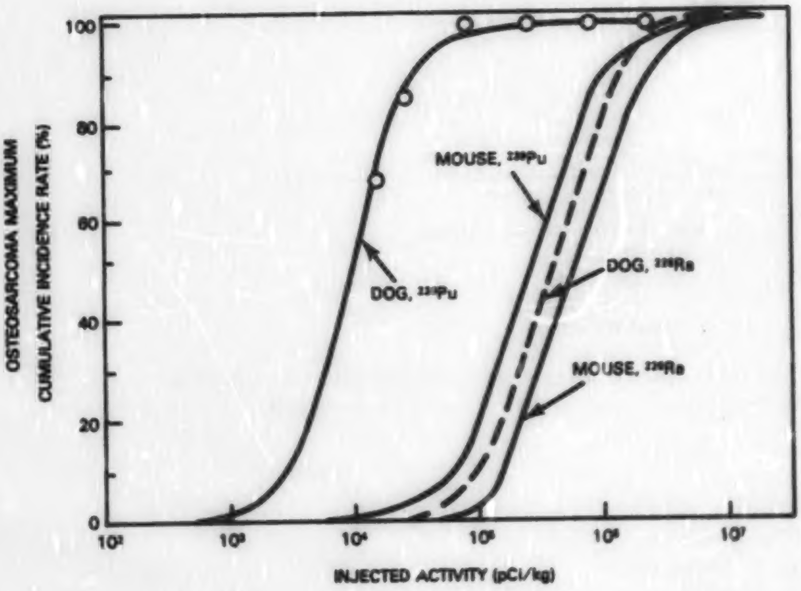

FIGURE A.II-24

Comparison of Plutonium-Induced Osteosarcomas in Mice and Dogs [50] might be 10/0.006%/rem^{-1} or 1666 rem (167 rad)*; 440/1500 ≃ 167/x, or x = 570 rad/10%. The human lung cancer estimate related to the bone comparison would be 0.0018%/rem.

The Quality Factor Model

The relative carcinogenicity of alpha particles in animal lungs can be compared to effects from low LET (β-γ, X) irradiation, but the human radionuclide data to complete the comparison is lacking. The precision and accuracy of the dosimetry in the uranium and fluorspar miner data are severely deficient and the possible role of inhaled co-carcinogens is unknown [93]. Most of the dose estimates for effects range from 2,000 to 20,000 rem.

That the incidence of lung tumors in animals is not linear with respect to dose is seen in Figure A.II-25 for low LET radiation and Figure A.II-26 for alpha-emitters [92]. A comparison of the effectiveness of the two types of radiation is shown in Figure A.II-27 where for the same level of effect the two types of radiation differ by a factor of about 5 for the low doses and by about 20 for high doses. If the QF of 10 is applied to the alpha dose curve (and a QF of 1 for β, γ and x-rays), it would appear that the two curves would almost superimpose. Again noting the 10% incidence merely for comparative purposes, the 100 rad alpha value multiplied by the QF of 10 is about equal to the β - γ value of about 1000 rad (rem). The inconstancy of the relationship is shown by the lack of complete parallelism between the two curves in Figure A.II-27.

As in Jacobi's bone comparison for radium, lungs also may respond nonlinearly when subjected to continued low dose rate alpha irradiation. The limited data on uranium miners also suggest a nonlinear response [99].

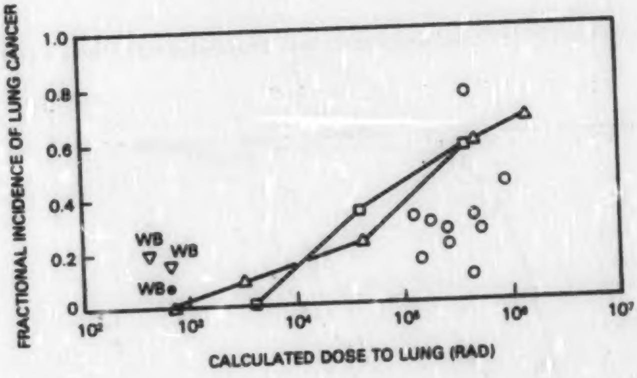

FIGURE A.II-25

Fractional Incidence of Lung Cancer in Animals Exposed to low LET (β,X,γ) Radiation from Implanted Sources and X-Radiation from External Sources [92]

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*In computing this from the 90% incidence value in dogs, no consideration is given to the occurrence of multiple tumors in the dogs.

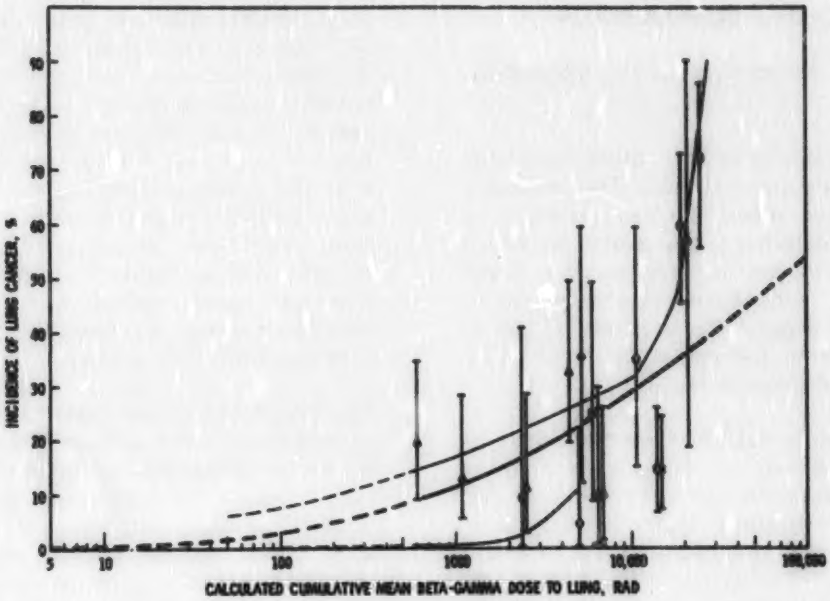

FIGURE A.II-26

Relationship Between Incidence of Lung Cancer and Radiation Dose to Lung from Inhaled Beta-Gamma Emitting Radionuclides in Experimental Animals [48]

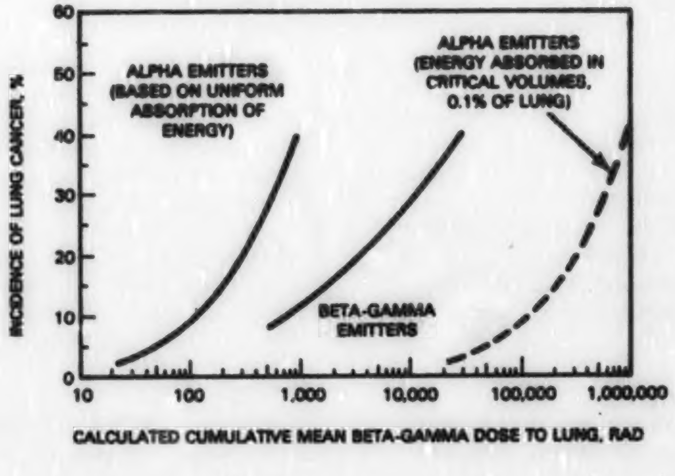

FIGURE A.II-27

Comparative Relationships Between the Incidences of Lung Cancer and Radiation Doses from Inhaled Beta-Gamma and Alpha Emitters in Experimental Animals [92]

MECHANISMS OF CARCINOGENESIS*

Carcinogenic Mechanisms at the Intracellular Level

The cellular processes that cause neoplastic transformations are unknown. The efficiency of carcinogenic action is clearly affected by factors that determine the extent to which a given carcinogen actually reaches target cells and the susceptibility to transformation. Susceptibility depends on a variety of factors which determine the extent of initial injury and the effectiveness of repair.

At present, it is not clear whether there is a common pathway for different carcinogens for cellular neoplastic transformation, although this has been suggested in terms of the activation of a latent viral oncogen [102,103]. It is also not clear whether the inheritable abnormalities transmitted to successive generations of proliferating cancer cells are caused by genetic damage or abnormal differentiation involving deranged expression of the normal genome. Neoplastic transformation at the cellular level is not a simple all-or-none phenomenon. Transformed cells show differences in the extent to which they acquire the several independent properties of neoplasia: unrestrained proliferation, invasiveness, and antigenicity.

Neoplasia is also not an immutable property which is transmitted equally to all the progeny of a transformed cell. The clonal outgrowth of single cultured cells shows a spectrum of neoplastic and nonneoplastic properties amongst progeny cells which has been related to chromosomal balance. Single cells isolated from malignant teratomas also produce clones of cells, some of which are neoplastic and others of which undergo normal differentiation. The neoplastic character of a tumor, therefore, appears to depend on the average behavior of its component cells.

It is possible that the carcinogenic process will prove to be similar to that of species evolution, in that random genetic damage of somatic cells produced by carcinogens is combined with selection pressures to breed out a race of cells having growth advantages over their normal counterparts. It would be expected that the process would be generally slow, progressive in character and wasteful of cells due to lethal injury; cell lethality, however, could undoubtedly facilitate the selection process, especially in tissues which normally have a low proliferative rate.

Pitot and Heidelberger [104] have formulated an epigenetic scheme for neoplasia based on abnormal differentiation. Braun [105] has also elaborated on this alternative based on plant tumorigenesis experiments. These studies show that plant tumors can arise from an epigenetic differentiation abnormality which is characterized by the production of large amounts of growth hormone by the tumor cells. These anaplastic tumors, after years of propagation in tissue culture, can permanently revert to normal plant tissue when grown under certain conditions.

The Problem of So-Called "Precancerous" Lesions

The problem of so-called "precancerous" lesions applies also to terms such as "preneoplastic", "pretumorous", and "preadenomatous" and to the question of whether benign tumors should be considered precancerous lesions.

According to Ewing [106], precancerous lesions are those which precede and favor the development of cancer but do not possess the essential elements of the cancerous process.

It must be pointed out that there is nothing in the histologic picture of these lesions that indicates which of them will "precede and favor the development of cancer." It is the ulterior development of similar lesions that is brought to mind when such a prediction is made [107]. The concept of precancerous lesions is purely statistical and certainly not applicable pathognomonically in individual cases.

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*Prepared for the Committee's use by G. W. Casarett

Although most so-called precancerous lesions are proliferative in nature, there are many other lesions, even more proliferative, which are not precancerous **[108]**. Likewise, in addition to proliferative changes, many of the so-called precancerous lesions are also characterized by tissue disorganization, vascular changes and fibrosis, but so are many other lesions which are not precancerous. These changes, or combinations of changes, might have tumorigenic-enhancing or promoting influence, but they more likely represent the various ways in which tissues can respond to severe acute or chronic damage rather than essential changes that assure cancer development. If the latter were true, the cancer incidence would be vastly greater than it is.

Perez-Tamayo **[107]** lists many diseases which have been regarded as precancerous, about half of which (in the total list) have been shown to be incorrect. Not even the presence of a benign tumor is necessarily indicative of increased probability of cancer development.

In order to qualify strictly as a precancerous lesion, even in the statistical sense, there must be a clear quantitative relationship between the precisely defined lesion (which must not possess essential elements of the cancerous process) and consequently a significantly enhanced incidence of cancer.

Once the statistical relationship has been established through observation of behavior of different lesions, the microscopic diagnosis may aid in assessing the possibility of cancer development, but not because of any peculiar histologic markings.

The terms "precancerous", "preadenoma" and the like have been used somewhat casually to indicate changes reminiscent of those preceding or concomitant with tumor development, to enhance descriptions of certain changes by describing them as "precancerous" or "preadenomatous", or to imply the possibility of subsequent tumor development when there is uncertainty as to the presence of essential features of the tumorous process in the lesions.

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APPENDIX B

PROCEDURES FOR COMMITTEE APPOINTMENTS AND CONSIDERATION OF POTENTIAL BIAS OF MEMBERS

As a general rule, individuals are appointed to NRC committees by the chairman, staff officers, and members of the NRC division and assembly concerned. (Division members are nominated by scientific societies in their relevant fields and, less frequently, by governmental agencies.)

The appointment process usually involves two or three layers of personal consultation between the selectors and people who are actively working in the pertinent fields. Typically, the assembly/division chairman or executive director approaches an individual in academia or industry whom he believes to be well informed about activities in his field and solicits his help in identifying potential members for the committee or panel. On the basis of such suggestions, the chairmen select a balanced membership and recommend it to the President of the National Academy of Sciences for his approval.

The President's office examines the nomination list with the following criteria in mind: balance, qualifications, and present commitments of the nominees to other committees and panels of the Academy and Research Council. Although a number of persons serve on two or even more NRC committees at a time, it is a general practice to limit the assignments to prevent overburdening a committee member.

NRC committee members are, in general, chosen for their technical qualifications, recognized communication skills, and judgmental qualities, but other more subjective factors, such as motivation and temperament, are not overlooked. The identification of possible members and the final committee selection are often preceded by an extensive analysis of the various competences needed to deal with the subject and issues being considered.

The appointing function is thus carried out at two levels: at the assembly and division level, where there is professional expertise in the scientific fields and the specific problems, and in the Executive Office of the Academy, where the above-mentioned screening procedure takes place. The Executive Office maintains a complete file of all current task appointments for all activities of the National Academy of Sciences and the National Research Council.

CONFLICT OF INTEREST

Organizations avoid knowingly appointing a person to a committee if his interests, or those of his employer, will be affected by actions of the committee. Awards committees, for example, should not include scientists whose academic departments are applicants for awards in the programs being considered. Industrial scientists should not sit as members of committees when the recommendations are likely to affect the business interests of their companies. Other forms of conflict of interest—ownership of equities in a company, industrial consultancies, and the like—also must be considered.

The problem becomes especially difficult when a field is so highly specialized that only a few top quality advisers can be found, and when the activities of the agency requesting advice are so pervasive in a field of expertise that almost all advisers with the technical competence required are or have been related to the agency in some way. This is a far from rare occurrence; examples are the relationship of the Atomic Energy Commission (now Energy Research and Development Administration) to the field of nuclear reactor development, of the National Institute of Health to policies for the support of biomedical education, and of the National Aeronautics and Space Administration to exobiology.

Where, for any reason, conflicts of interest must be accepted in order to obtain adequate expertise, it is important that they be known to all members of the committee and to the sponsoring and requesting agencies. This not only ensures that possible biases are recognized, but also assists members who have such conflicts to make necessary compensations in their own thinking and judgment.

Clear statements of the task assigned the committee, and of any possible conflicts of interest among its members, can do much to assure the likelihood of public confidence in its conclusion.

The following brief biographical sketches of the members of the ad hoc Committee on "Hot Particles" are included to demonstrate the expertise and competence of each member. Some of these may, in their background, demonstrate sources of possible bias, as discussed above. However, NAS/NRC and the Committee itself believe that in all official deliberations, the members have exercised their best scientific judgements. If any bias existed, it was manifested in a critical examination of each member's prior public statements and positions.

ALBERT, ROY E.

DATE OF BIRTH: 1924

EDUCATION:

A.B.	1944	Columbia College
M.D.	1946	New York University College of Medicine
	1946-47	Internship, Bellevue Hospital, Third Medical Division
	1949-51	USPHS Fellowship in Cardiovascular Hemodynamics, New York University College of Medicine
	1951-52	Residency in Medicine, University of the State of New York at Syracuse University Hospital

PAST POSITIONS:

1959-66	Associate Professor, Institute of Environmental Medicine, New York University Medical Center.
1956-59	Assistant Clinical Professor of Medicine (Geographical Full-Time) and Assistant Director of the Radioisotope Laboratory, George Washington University School of Medicine.
1954-56	Assistant Chief (1954-55), Chief (1955-56), Medical Branch, U.S. Atomic Energy Commission, Division of Biology and Medicine.
1952-54	Medical Officer, Health Safety Laboratory, New York Operations Office, U.S. Atomic Energy Commission.
1947-49	A.U.S. Medical Field Research Laboratory, Fort Knox, Kentucky (Military Service).

PRESENT POSITION:

Director, Office of Health Ecological Effects, Environmental Protection Agency (July 1975 -).

Professor of Environmental Medicine (1966 -)—on sabbatical leave.

Vice Chairman and Deputy Director of Institute of Environmental Medicine, New York Univ. Medical Center (1973 -)—on sabbatical leave.

PUBLICATIONS:

Sixty-three journal articles, chiefly on physiology, biology, carcinogenesis, radiation biology, and radiation effects.

CONSULTANTSHIPS:

Task Force II, National Conference on Preventive Medicine (1975 -) (American College of Preventive Medicine and NIH Fogarty Center).

AIBS Life Sciences Study Team for Assessment of Ecological Impact (1974 -) (American Institute of Biological Sciences).

Study on Principles of Decision-Making for Regulating Chemicals in the Environment (1974 -) (National Academy of Sciences—National Research Council).

CONSULTANTSHIPS (Continued):

Task Group on the Influence of Radiobiological Factors in the Estimation of Risks of Cancer Induction for Purposes of Radiation Protection (1974 -) (International Commission on Radiological Protection).

Committee on Biologic Effects of Atmospheric Pollutants - Panel on Arsenic (1973 -) (National Academy of Sciences—National Research Council).

Advisory Committee to the Radiation Registry of Physicians (1972 -) (National Academy of Sciences—National Research Council).

NCRP Scientific Committee 38 - Task Group on Krypton-85 (1972 -) (National Council on Radiation Protection and Measurements).

Committee on Biologic Effects of Atmospheric Pollutants - Panel on Airborne Particles (1972 -) (National Academy of Sciences—National Research Council).

Committee on Toxicology, ad hoc Panel on Carbon Monoxide (1971 -) (National Academy of Sciences—National Research Council).

Committee on Biologic Effects of Atmospheric Pollutants, Panel on Polycyclic Organic Matter (1970-72) (National Academy of Sciences—National Research Council).

Ad hoc Committee on Environmental Health Research, Panel on Hazardous Trace Substances (1970-72) (Office of Science and Technology, Executive Office of the President).

Ad hoc Subcommittee on Asbestos Hazards (1970) (Air Pollution Working Group of the New York City Health Research Council).

Ad-hoc Committee on Air Quality Standards in Space Flight (1967) (National Academy of Sciences—National Research Council).

Committee on Research in the Life Sciences, Panel on Environmental Health (1967) (National Academy of Sciences—National Research Council).

Air Pollution Advisory Committee (1967-70) (New York City Department of Health).

Division of Biology and Medicine Committee on Space Nuclear Systems and Radiological Safety Matters (1967 -) (U.S. Atomic Energy Commission).

Technical Advisory Committee on Uranium Mining Studies (1966) (Department of Health, Education, and Welfare).

Consultant to the Surgeon General's Advisory Committee on Smoking and Health (1963).

ALPEN, EDWARD L.

DATE OF BIRTH: 1922

EDUCATION:

B.S.	1946	Chemistry, University of California, Berkeley
Ph.D.	1950	Pharmaceutical Chemistry and Pharmacology, University of California, San Francisco

PAST POSITIONS:

1972-75	Director, Pacific Northwest Division, Battelle Memorial Institute, Richland, Washington.
1971-72	Associate Director, Pacific Northwest Laboratories, Battelle Memorial Institute, Richland, Washington.
1969-71	Manager, Environmental and Life Sciences Division, Battelle Pacific Northwest Laboratories.
1958-69	Head, Biological and Medical Sciences Division, Naval Radiological Defense Laboratory.
1954-58	Head, Biophysics Branch, Naval Radiological Defense Laboratory.
1951-54	Scientific Investigator, Naval Radiological Defense Laboratory.
1950-51	Assistant Professor of Pharmacology, George Washington University School of Medicine, Washington, D.C.
1946-47	Research Chemist, Cutter Laboratories, Berkeley, California.

PRESENT POSITION:

Director, Donner Laboratory, University of California, Berkeley, California.

PUBLICATIONS:

Approximately 70 journal publications chiefly on radiation effects, biology, aging, neurophysiology, psychology, biophysics, and immunology.

HONORS AND/OR CITATIONS:

Senior Post-Doctoral Fellow of the National Science Foundation, Oxford University, Oxford, England (in residence 1958-59).

Sustaining Members Award for Creative Research of the Association of Military Surgeons (1961).

Distinguished Achievement in Science Gold Medal and Citation, Department of the Navy (1962).

Distinguished Service Gold Medal and Citation, Department of Defense (1963).

PROFESSIONAL AFFILIATIONS:

National Councillor, Radiation Research Society (1952 -).

Member, Board of Editors, Society for Experimental Biology and Medicine.

Member, American Physiological Society (1952 -).

Member, National Environmental Council, Dept. of HEW (1970-74).

Chairman, Biological Effects Advisory Panel, Bureau of Radiological Health (1968-74).

Member, Sigma Xi. Local chapter president (1963-64).

Fellow, California Academy of Sciences.

Foreign Associate Member, Royal Society of Medicine (1962 -).

Member, Radiation Study Section, National Institutes of Health (1960-72).

Member, Advisory Panel to Collaborative Radiological Health Laboratory, U.S. Public Health Service (1965-70).

Member, Quadripartite Technical Cooperation Panel (U.S., U.K., Canada, Australia, Scientific Cooperation Group of Defense).

Councillor, National Council on Radiation Protection (1955-74).

Board of Directors, National Council on Radiation Protection (1972-74).

Member, NCRP Scientific Committees 14 and 24: Chairman, NCRP SC 39.

Consultant to the Director, Clinical Investigation Center, U.S. Naval Hospital, Oakland (1956 -).

Member, 'Failla' Panel to the Department of Defense on Radiological Instrumentation (1955-61).

BAIR, WILLIAM J.

DATE OF BIRTH: 1924

EDUCATION:

B.A.	1949	Chemistry, Ohio Wesleyan University
Ph.D.	1954	Radiation Biology, University of Rochester

PAST POSITIONS:

1973-75	Director, Life Sciences Program, Pacific Northwest Laboratories, Battelle Memorial Institute, Richland, Washington.
1968-75	Manager, Biology Department, Pacific Northwest Laboratories, Battelle Memorial Institute, Richland, Washington.
1956-68	Manager, Inhalation Toxicology Section, Biology Department, General Electric Company, Richland, Washington (prime contractor changed to Battelle Memorial Institute in 1965 - position unchanged).
1954-56	Biological Scientist, General Electric Company, Richland, Washington.
1950-54	Research Associate, Radiation Biology, University of Rochester.
1949-50	National Research Council, AEC Fellowship in radiological physics, University of Rochester.

PRESENT POSITION:

Manager, Environmental and Safety Research Program, Pacific Northwest Laboratories of Battelle Memorial Institute, Richland, Washington (March 1975 -).

PUBLICATIONS:

87 Journal articles or books chiefly on radiation biology, with emphasis on toxicity of inhaled radionuclides and pulmonary effects in experimental animals.

HONORS AND/OR CITATIONS:

E. O. Lawrence Memorial Award by the U.S. Atomic Energy Commission for research on radiation biology of inhaled radionuclides (1970).

AEC Fellowship in Radiological Physics, U. of Rochester, 1949-50.

PROFESSIONAL AFFILIATIONS:

Staff Member, Joint Center for Graduate Study at Hanford (operated by Oregon State University, Washington State University, and University of Washington). Lecturer in Radiation Biology (1955 -).

Member, International Commission on Radiological Protection, Committee 2 (1973 -).

PROFESSIONAL AFFILIATIONS (Continued):

Chairman, Task Group on the Biological Effects of Inhaled Radioactive Particles, International Commission on Radiological Protection (1969 -).

Chairman, Transuranium Technical Group (organized by the American Institute of Biological Sciences to advise the U.S. Atomic Energy Commission on biomedical research on transuranium elements) (1972 -).

Member of National Council on Radiation Protection and Measurement (NCRP) (1974 -).

Member, Board of Directors, National Council on Radiation Protection and Measurement (NCRP) (1976 -).

Member of Scientific Committee 1 (NCRP) on Basic Radiation Protection Criteria (1975 -).

Member of Scientific Committee 34 (NCRP) on Maximum Permissible Concentration for Occupational and Non-Occupational Exposure (1970-).

Chairman of NCRP ad hoc Committee on "Hot Particles" (1974-75).

Member of Subcommittee on Inhalation Hazards of the Committee on Pathologic Effects of Atomic Radiation, National Academy of Science (1957-64).

Member of National Academy of Sciences/National Research Council ad hoc Committee on "Hot Particles" of the Advisory Committee on the Biological Effects of Ionizing Radiation (1974 -).

Chairman, Mound Laboratory Internal Emitter Working Group, Division of Biomedical and Environmental Research, U.S. Energy Research and Development Administration (1975-76).

Member, the Nevada Applied Ecology Group ad hoc Pu Committee, AEC-ERDA (1970 -).

Member, Joint Space Nuclear System/Biomedical and Environmental Research Working Group, Atomic Energy Commission (1967-73).

Member, Radiation Research Society (1954 -).

Member, the Health Physics Society (1956 -). Board of Directors (1970-73).

Member, Society for Experimental Biology and Medicine (1973 -). Vice Chairman, Northwest Section (1967-70, 1974-76).

Member, Sigma Xi (1953 -). Vice Chairman, Tri-Cities, Washington Club (1973-74).

Member, Reticuloendothelial Society (1960 -).

CASARETT, GEORGE W.

DATE OF BIRTH: 1920

EDUCATION:

1938-41	University of Toronto (pre med.)
1943-45	University of Rochester (pre med.)
1948-52	University of Rochester (graduate school in medicine)
1952	Ph.D.

PAST POSITIONS:

1959-63	Associate Professor in Radiation Biology. Chief, Radiation Pathology Section, Atomic Energy Project. Chief, Radiation Pathology Section, Radiation Therapy Department.
1957-59	Assistant Professor in Radiation Biology Department Scientist (Rad. Path.) Atomic Energy Project.
1953-57	Instructor in Radiation Biology Department. Scientist (Rad. Path.) Atomic Energy Project.
1947-53	Chief of Pathology Unit and Assistant Chief of Radiation Tolerance Section, Atomic Energy Project.
1943-47	Research Assistant in Pathology Division, Manhattan Project.

PRESENT POSITION:

Professor of Radiology (secondary appointment). Director of Experimental Research in Clinical Radiation Research Center.

Professor of Radiation Biology and Biophysics (primary appointment). Head of Radiation Pathology Section of Atomic Energy Project.

PUBLICATIONS:

175 Journal articles, book chapters, reports, or books, chiefly on radiation pathology, radiation biology, carcinogenesis, cancer biology, and gerontology.

HONORS AND/OR CITATIONS:

Co-winner (with collaborators) of First Award and Silver Roentgen Medal, Meeting of American Roentgen Ray Society Meeting, 1959.

Co-winner (with collaborators) of First Award (cum laude) for Fundamental Research, Annual Meeting of Radiological Society for North America, 1959, 1964, 1971.

CURRENT CONSULTANTSHIPS:

Chairman of National Academy of Sciences Advisory Committee on Biological Effects of Ionizing Radiations. (Formerly member of NAS Advisory Committee to Federal Radiation Council.)

Member of Board of Directors of National Council on Radiation Protection and Measurement (NCRP).

Chairman of Scientific Committee 14 of National Council on Radiation Protection and Measurement (NCRP).

Chairman of NCRP ad hoc Committee on Comparison of Radiation Protection Philosophies.

Member of National Cancer Institute Cancer Research Training Committee. (Committee inactive at present.)

Consultant to Task Group on Biological Effects of Inhaled Particulates, of International Commission on Radiological Protection.

EPP, EDWARD R.

DATE OF BIRTH: 1929

EDUCATION:

B.A.	1950	University of Saskatchewan
M.A.	1952	University of Saskatchewan
Ph.D.	1955	McGill University

PAST POSITIONS:

Sloan-Kettering Institute for Cancer Research		Dept. of Biophysics, Sloan-Kettering Division, Graduate School of Medical Sciences, Cornell University	
1973—74	Laboratory Head	1970-74	Professor (Dept.)
1969-74	Member	1966-72	Chairman (Dept.)
1968-72	Chief, Div. of Physical Biology	1966-70	Assoc. Professor
1964-69	Assoc. Member	1960-66	Asst. Professor
1960-64	Associate	1958-60	Associate
1957-60	Assistant	1957-58	Assistant

1967-74	Associate Attending Physicist, Dept. of Medical Physics, Memorial Hospital for Cancer and Allied Diseases.
1956-57	Consultant Physicist, Dept. of Radiology, Montreal Children's Hospital.
1955-57	Radiation Physicist, Department of Radiology, Montreal General Hospital.
1952-53	Scientific Staff, National Research Council of Canada
1949-50	Summer Research Assistant, Physics Dept., University of Saskatchewan.

PRESENT POSITION:

Radiation Biophysicst and Head, Division of Radiation Biophysics, Massachusetts General Hospital (1974 -).

Professor of Radiation Therapy (Radiation Biophysics), Faculty of Medicine, Harvard University (1974 -).

PUBLICATIONS:

33 Journal articles chiefly on radiation physics and radiation biology.

CURRENT CONSULTANTSHIPS:

Radiation Study Section of NIH (1971-75).

Editorial Board, Radiation Research Journal (1972-75).

Chairman, Scientific Program Committee-AAPM (1972 -).

Councillor in Physics, Radiation Research Society (1974 -).

GOLDMAN, MARVIN

DATE OF BIRTH: 1928

EDUCATION:

A.B.	1949	Adelphi University (Biology)
M.S.	1951	University of Maryland (Zoology-Physiology)
Ph.D.	1957	University of Rochester (Radiation Biology)

PAST POSITIONS:

1972-73	Principal Investigator, Studies on Canine Bone Density, NASA, (NAS2-6763), University of California, Davis. Biophysicist-Physiologist, Division of Biomedical and Experimental Research, U.S. Atomic Energy Commission. Associate Director for Sciences, UCD
1971-72	Consultant, General Electric Company
1970-71	Principal Investigator, Studies on ^{90}Sr Toxicity in Mice, USPHS, UCD.
1968-71	Collaborator, Orbital Flight Effects on Calcium Kinetics and Fracture Healing Repair, NASA (NAS2-5057), UCD.
1958-64	Associate Radiobiologist, UCD.

PRESENT POSITION:

Director, Radiobiology Laboratory, UCD (1973 -).

Professor of Radiobiology, Department of Radiological Sciences, School of Veterinary Medicine and Department of Radiology, School of Medicine, UCD (1973 -).

Research Radiobiologist, Radiobiology Laboratory, UCD (1964 -).

PUBLICATIONS:

101 Journal articles, book chapters, reports, or books, chiefly on radiation pathology, radiation biology and carcinogenesis.

HONORS AND/OR CITATIONS:

E. O. Lawrence Memorial Award presented by the U.S. Atomic Energy Commission (1972).

CURRENT CONSULTANTSHIPS:

Council Member, National Council on Radiation Protection and Measurements (1974 -).

Chairman, U.S. Atomic Energy Commission, DSNS/DBER Biomedical Working Group (1973 -).

Member, University of California Cancer Research Coordinating Committee (1973 -).

Co-principal Investigator, Tumor Biology Training Grant, NIH/NCI (1972 -).

Member, Advisory Committee, Crocker Nuclear Laboratory, University of California, Davis (1971 -).

GREGG, EARLE C.

DATE OF BIRTH: 1918

EDUCATION:

B.S.	1940	Case Institute of Technology, Cleveland
M.S.	1942	Case Institute of Technology, Cleveland
Ph.D.	1949	Case Institute of Technology, Cleveland (Physics)

PAST POSITIONS:

1958-65	Associate Professor of Radiology (Radiation Physics), Case Western Reserve University.
1952-58	Associate Professor of Physics, Case Institute of Technology
1949-52	Assistant Professor of Physics, Case Institute of Technology
1946-49	Instructor in Physics, Case Institute of Technology
1943-46	Research Associate, Columbia University
1942-43	Research Associate, Massachusetts Institute of Technology

PRESENT POSITION:

Professor of Radiology (Radiation Physics), Case Western Reserve University (1965 -).

Chief, Radiologic Physics, Department of Radiology, University Hospitals.

Chief, Biophysics Section, Division of Radiation Biology, Case Western Reserve University.

Chairman, Biophysics Graduate Study Program, Case Western Reserve University.

Committee on Human Use of Radioisotopes, University Hospitals.

Chairman, Committee on Biophysics, Case Western Reserve University.

Visiting Staff, Metropolitan General, St. John's, Highland View, and Lutheran Hospitals.

PUBLICATIONS:

107 Journal articles chiefly on biophysics, ultrasonics, radiologic physics and nuclear physics.

HONORS AND/OR CITATIONS:

Member of Editorial Board, Investigative Radiology.

Fellow, American Physical Society.

Standards Committee, American College of Radiology.

Past Editor, Journal Applied Physics.

Scientific Committee, American Association Physics in Medicine.

HONORS AND/OR CITATIONS (Continued):

Registered Professional Engineer, State of Ohio.

Member, Radiation Study Section, National Institutes of Health.

Committee on Radiology, National Academy of Sciences.

Member, Cancer Research Center Review Committee, National institutes of Health.

Member, Advisory Committee on the Biological Effects of Ionizing Radiations (BEIR), National Academy of Sciences.

Chairman, Division of Biological Physics, American Physical Society.

LEWIS, EDWARD B.

DATE OF BIRTH: 1918

EDUCATION:

B.S.	1939	University of Minnesota
Ph.D.	1942	California Institute of Technology

PAST POSITIONS:

1956-66	Professor, California Institute of Technology.
1949-56	Associate Professor, California Institute of Technology.
1948-49	Assistant Professor, California Institute of Technology
1948-49	Rockefeller Foundation Fellow, School of Botany, Cambridge University, Cambridge, England.
1946-48	Instructor in Genetics, California Institute of Technology.
1942-45	U.S. Army Air Force meteorologist and oceanographer.

PRESENT POSITION:

Thomas Hunt Morgan Professor, California Institute of Technology (1966 -).

PUBLICATIONS:

21 Journal articles chiefly on genetics of drosophila and carcinogenic effects of ionizing radiation on human populations.

HONORS AND/OR CITATIONS:

Member, National Academy of Sciences (1968 -).

Genetics Society of America (Secretary 1962-64) (Vice President 1966) (President 1967).

Fellow, American Association for the Advancement of Science.

American Academy of Arts and Sciences.

American Society of Human Genetics.

CONSULTANTSHIPS:

National Council for Radiation Protection and Measurements.

Advisory Committee on the Biological Effects of Ionizing Radiation, National Research Council - National Academy of Sciences.

McCLELLAN, ROGER O.

DATE OF BIRTH: 1937

EDUCATION:

1960	Doctor of Veterinary Medicine with Highest Honors, Washington State University

PAST POSITIONS:

1966-73	Assistant Director of Research and Director, Fission Product Inhalation Program, Lovelace Foundation for Medical Education and Reasearch, Albuquerque, New Mexico.
1965-66	Scientist, Medical Research Branch, Division of Biology and Medicine, U.S. Atomic Energy Commission, Washington, D.C.
1965-	Senior Scientist, Biology Department, Pacific Northwest Laboratories, Battelle Memorial Institute, Richland, Washington (leave of absence to the U.S.A.E.C.)
1963-64	Senior Scientist, Biology Laboratory, Hanford Laboratories, General Electric Company, Richland, Washington.
1959-62	Biological Scientist, Biology Laboratory, Hanford Laboratories, General Electric Company, Richland, Washington.
1957-58	(Summers) - Junior Scientist, Biology Laboratory, Hanford Laboratories, General Electric Company, Richland, Washington.
1957-60	Research Assistant, Department of Veterinary Microbiology, Washington State University, Pullman, Washington.

PRESENT POSITIONS:

Vice President and Director of Research Administration and Director, Inhalation Toxicology Research Institute, Lovelace Foundation for Medical Education and Research, Albuquerque, New Mexico.

PUBLICATIONS:

192 Scientific publications, technical reports or abstracts on various aspects of the metabolism, toxicity and internal dosimetry of radionuclides in experimental animals.

HONORS AND/OR CITATIONS:

Elda E. Anderson Award, Health Physics Society (1974).

CONSULTANTSHIPS:

Member, ad hoc Committee on "Hot Particles", Advisory Committee on the Biological Effects of Ionizing Radiations (BEIR), National Research Council (1974 -).

Member, North American Late Effects Group Steering Committee (1974 -).

CONSULTANTSHIPS (Continued):

Chairman, Environmental Radiation Exposure Advisory Committee Member, Scientific Advisory Board, Environmental Protection Agency (1974 -).

Member, National Institutes of Health, Animal Resources Advisory Committee (1974-78).

Member, Environmental Radiation Exposure Advisory Committee of the Environmental Protection Agency (1972 -).

Member, Transuranium Technical Group (Advisory to U.S. Atomic Energy Commission, Division of Biomedical and Environmental Research) (1972 -).

Member, National Council on Radiation Protection and Measurements (1971 -).

Program Committee Member and Chairman, Health Physics Society (1970-73).

President, American Board of Veterinary Toxicology (1970-73).

Member, Subcommittee on Whole Animal Radiobiology and Pathology, Los Alamos Meson Physics Facility (LAMPF) (1970 -).

Chairman, Scientific Committee #30 of National Council on Radiation Protection and Measurements (1969 -).

Member, Toxicology Study Section, National Institutes of Health (1969-73).

Consultant, National Institute of Environmental Health Sciences, National Institutes of Health (1968-71).

Councilman, American College of Veterinary Toxicologists (1968-71).

Advisor, Laboratory Animal Biology and Medicine Training Program, University of California, Davis (1968-70).

Member, Joint Space Nuclear Systems/Biomedical and Environmental Research Working Group (1967-73).

RADFORD, EDWARD P.

DATE OF BIRTH: 1922

EDUCATION:

	1937-40	Phillips Exeter Academy, Exeter, New Hampshire
	1940-43	Massachusetts Institute of Technology
	1943-46	Harvard Medical School
M.D.	1946	Harvard Medical School

PAST POSITIONS:

1965-68	Professor and Director, Department of Environmental Health Director of Kettering Laboratory Professor of Physiology, College of Medicine, University of Cincinnati.
1959-65	Associate Professor of Physiology, Harvard School of Public Health.
1955-59	Physiologist, Haskell Laboratory for Toxicology and Industrial Medicine, E. I. duPont de Nemours and Company, Newark, Delaware.
1952-55	Associate, Department of Physiology, Harvard School of Public Health.
1950-52	Instructor, Department of Physiology, Harvard Medical School.
1949-50	Teaching Fellow, Department of Physiology, Harvard Medical School.
1947-49	Active Duty, U.S. Air Force, Chief of Medical Service, Maxwell Air Force Base, Montgomery, Alabama.
1946-47	Rotating Internship, Geisinger Memorial Hospital, Danville, Pennsylvania.

PRESENT POSITION:

Professor of Environmental Medicine, School of Hygiene and Public Health, Johns Hopkins University (1968 -).

PUBLICATIONS:

Several scientific journal articles and published testimony before legislative bodies chiefly on radiation biology, health effects of environmental pollutants, and carcinogenesis.

HONORS AND/OR CITATIONS:

National Scholar, Harvard Medical School (1943-46).

Macy Faculty Scholar Award (1975-76).

CONSULTANTSHIPS:

Medical Consultant to Council on Environmental Quality, Washington, D.C. (1975 -).

Consultant in Occupational Health, State of Maryland, Division of Labor and Industries (1973 -).

CONSULTANTSHIPS (Continued):

Faculty Member, Westinghouse International School of Environmental Management, Ft. Collins, Colorado (1972 -).

Consultant to Department of Anesthesiology, Massachusetts General Hospital, Boston, Massachusetts (1963 -).

National Academy of Sciences Committee on Medical and Biological Effects of Environmental Pollutants, Subcommittee on Carbon Monoxide.

National Academy of Sciences Advisory Committee on the Biological Effects of Ionizing Radiations, ad hoc Committee on "Hot Particles."

Advisory Council, Bureau of Air Quality Control, State of Maryland.

Radiation Control Advisory Board, State of Maryland.

Chairman, Power Plants and Human Health and Welfare Studies Group, Department of Natural Resources, State of Maryland (1972-73).

Member, National Academy of Sciences Advisory Committee on the Biological Effects of Ionizing Radiation (1970-72).

Member, The Governor's Advisory Council on Nuclear Reactors, State of Pennsylvania (1973-74).

APPENDIX C

COMMITTEE MEETINGS AND ATTENDANCE

November 14, 1974

Committee Members

Albert, Dr. Roy E., New York University Medical Center, New York, N.Y.—Chairman

Alpen, Dr. Edward L., Battelle Pacific Northwest Laboratory, Richland, Wash.

Bair, Dr. William J., Battelle Pacific Northwest Laboratory, Richland, Wash.

Casarett, Dr. George W., University of Rochester Medical Center, Rochester, N.Y.

Epp, Dr. Edward R., Massachusetts General Hospital, Boston, Mass.

Goldman, Dr. Marvin, University of California, Davis, Calif.

Gregg, Dr. Earle C., University Hospital, Cleveland, Ohio

Lewis, Dr. Edward B., California Institute of Technology, Pasadena, Calif.

McClellan, Dr. Roger O., Lovelace Foundation, Albuquerque, New Mexico

Guests

Ellett, Dr. William H., Environmental Protection Agency, Washington, D.C.

Mills, Dr. William A., Environmental Protection Agency, Washington, D.C.

Wachholz, Dr. Bruce W., Atomic Energy Commission, Washington, D.C.

National Academy of Sciences—Assembly of Life Sciences—Division of Medical Sciences

Hilberg, Dr. Albert W., Senior Staff Officer

McConnaughey, Dr. David A., Senior Staff Officer

January 30 - 31, 1975 - (Jan. 30)

Committee Members

Albert, Dr. Roy E., New York University Medical Center, New York, N.Y.—Chairman

Bair, Dr. William J., Battelle Pacific Northwest Laboratory, Richland, Wash.

Casarett, Dr. George W., University of Rochester Medical Center, Rochester, N.Y.

Epp, Dr. Edward R., Massachusetts General Hospital, Boston, Mass.

Goldman, Dr. Marvin, University of California, Davis, Calif.

Gregg, Dr. Earle C., University Hospital, Cleveland, Ohio

Lewis, Dr. Edward B., California Institute of Technology, Pasadena, Calif.

McClellan, Dr. Roger O., Lovelace Foundation, Albuquerque, New Mexico

Radford, Dr. Edward P., Johns Hopkins University, Baltimore, Maryland

Guests

Alexander, Mr. R. E., Nuclear Regulatory Comission, Washington, D.C.

Hobbs, Dr. Charles H., Lovelace Foundation, Albuquerque, New Mexico

Nelson, Dr. Neal S., Environmental Protection Agency, Washington, D.C.

Park, Dr. James F., Battelle Pacific Northwest Laboratory, Richland, Wash.

Sanders, Dr. Charles L., Battelle Pacific Northwest Laboratory, Richland, Wash.

Wachholz, Dr. Bruce W., Atomic Energy Commission, Washington, D.C.

National Academy of Sciences—Assembly of Life Sciences—Divison of Medical Sciences

Hilberg, Dr. Albert W., Senior Staff Officer

McConnaughey, Dr. David A., Senior Staff Officer

January 30 - 31, 1975 - (Jan. 31)

Committee Members

Albert, Dr. Roy E., New York University Medical Center, New York, N.Y.—Chairman

Bair, Dr. William J., Battelle Pacific Northwest Laboratory, Richland, Wash.

Casarett, Dr. George W., University of Rochester Medical Center, Rochester, N.Y.

Epp, Dr. Edward R., Massachusetts General Hospital, Boston, Mass.

Goldman, Dr. Marvin, University of California, Davis, Calif.

Gregg, Dr. Earle C., University Hospital, Cleveland, Ohio

Lewis, Dr. Edward B., California Institute of Technology, Pasadena, Calif.

Radford, Dr. Edward P., Johns Hopkins University, Baltimore, Maryland

Guests

Alexander, Mr. R. E., Nuclear Regulatory Commission, Washington, D.C.

Hobbs, Dr. Charles H., Lovelace Foundation, Albuquerque, New Mexico

Nelson, Dr. Neal S., Environmental Protection Agency, Washington, D.C.

Park, Dr. James F., Battelle Pacific Northwest Laboratory, Richland, Wash.

Sanders, Dr. Charles L., Battelle Pacific Northwest Laboratory, Richland, Wash.

Wachholz, Dr. Bruce W., Atomic Energy Commission, Washington, D.C.

National Academy of Sciences—Assembly of Life Sciences—Division of Medical Sceiences

Hilberg, Dr. Albert W., Senior Staff Officer

March 13 - 14, 1975 - (Mar. 13)

Committee Members

Albert, Dr. Roy E., New York University Medical Center, New York, N.Y.—Chairman

Bair, Dr. William J., Battelle Pacific Northwest Laboratory, Richland, Wash.

Casarett, Dr. George W., University of Rochester Medical Center, Rochester, N.Y.

Epp, Dr. Edward R., Massachusetts General Hospital, Boston, Mass.

Goldman, Dr. Marvin, University of California, Davis, Calif.

Gregg, Dr. Earle C., University Hospital, Cleveland, Ohio

McClellan, Dr. Roger O., Lovelace Foundation, Albuquerque, New Mexico

Radford, Dr. Edward P., Johns Hopkins University, Baltimore, Maryland

National Academy of Sciences—Assembly of Life Sciences—Divison of Medical Sciences

Hilberg, Dr. Albert W., Senior Staff Officer

Kennedy, Dr. Thomas J., Jr., Executive Director, Assembly of Life Sciences

Vosburg, Dr. Albert C., Associate Executive Director, Assembly of Life Sciences

March 13 - 14, 1975 - (Mar. 14)

Committee Members

Albert, Dr. Roy E., New York University Medical Center, New York, N.Y.—Chairman

Bair, Dr. William J., Battelle Pacific Northwest Laboratory, Richland, Wash.

Casarett, Dr. George W., University of Rochester Medical Center, Rochester, N.Y.

Epp, Dr. Edward R., Massachusetts General Hospital, Boston, Mass.

Goldman, Dr. Marvin, University of California, Davis, Calif.

Gregg, Dr. Earle C., University Hospital, Cleveland, Ohio

Lewis, Dr. Edward B., California Institute of Technology, Pasadena, Calif.

McClellan, Dr. Roger O., Lovelace Foundation, Albuquerque, New Mexico

Radford, Dr. Edward P., Johns Hopkins University, Baltimore, Maryland

National Academy of Sciences—Assembly of Life Sciences—Division of Medical Sciences

Hilberg, Dr. Albert W., Senior Staff Officer

May 21 - 22, 1975 - (May 21)

Committee Members

Albert, Dr. Roy E., New York University Medical Center, New York, N.Y.—Chairman

Alpen, Dr. Edward L., Battelle Pacific Northwest Laboratory, Richland, Wash.

Bair, Dr. William J., Battelle Pacific Northwest Laboratory, Richland, Wash.

Casarett, Dr. George W., University of Rochester Medical Center, Rochester, N.Y.

Epp, Dr. Edward R., Massachusetts General Hospital, Boston, Mass.

Gregg, Dr. Earle C., University Hospital, Cleveland, Ohio

Lewis, Dr. Edward B., California Institute of Technology, Pasadena, Calif.

McClellan, Dr. Roger O., Lovelace Foundation, Albuquerque, New Mexico

Radford, Dr. Edward P., Johns Hopkins University, Baltimore, Maryland

National Academy of Sciences—Assembly of Life Sciences—Division of Medical Sciences

Hilberg, Dr. Albert W., Senior Staff Officer

May 21 - 22, 1975 - (May 22)

Committee Members

Albert, Dr. Roy E., New York University Medical Center, New York, N.Y.—Chairman

Alpen, Dr. Edward L., Battelle Pacific Northwest Laboratory, Richland, Wash.

Bair, Dr. William J., Battelle Pacific Northwest Laboratory, Richland, Wash.

Casarett, Dr. George W., University of Rochester Medical Center, Rochester, N.Y.

Epp, Dr. Edward R., Massachusetts General Hospital, Boston, Mass.

Gregg, Dr. Earle C., University Hospital, Cleveland, Ohio

Lewis, Dr. Edward B., California Institute of Technology, Pasadena, Calif.

McClellan, Dr. Roger O., Lovelace Foundation, Albuquerque, New Mexico

Radford, Dr. Edward P., Johns Hopkins University, Baltimore, Maryland

National Academy of Sciences—Assembly of Life Sciences—Division of Medical Sciences

Hilberg, Dr. Albert W., Senior Staff Officer

Kennedy, Dr. Thomas J., Jr., Executive Director, Assembly of Life Sciences

Sitton, Mr. Paul L., Special Assistant to the NAS President

July 8 - 9, 1975 - (July 8)

Committee Members

Albert, Dr. Roy E., New York University Medical Center, New York, N.Y.—Chairman

Alpen, Dr. Edward L., Battelle Pacific Northwest Laboratory, Richland, Wash.

Bair, Dr. William J., Battelle Pacific Northwest Laboratory, Richland, Wash.

Casarett, Dr. George W., University of Rochester Medical Center, Rochester, N.Y.

Epp, Dr. Edward R., Massachusetts General Hospital, Boston, Mass.

Goldman, Dr. Marivn, University of California, Davis, Calif.

Gregg, Dr. Earle C., University Hospital, Cleveland, Ohio

Lewis, Dr. Edward B., California Institute of Technology, Pasadena, Calif.

McClellan, Dr. Roger O., Lovelace Foundation, Albuquerque, New Mexico

Radford, Dr. Edward P., Johns Hopkins University, Baltimore, Maryland

Guests

Cochran, Dr. Thomas B., Natural Resources Defense Council, Washington, D.C.

Ellett, Dr. William H., Environmental Protection Agency, Washington, D.C.

Tamplin, Dr. Arthur R., Natural Resources Defense Council, Washington, D.C

National Academy of Sciences—Assembly of Life Sciences—Division of Medical Sciences

Hilberg, Dr. Albert W., Senior Staff Officer

Kennedy, Dr. Thomas J., Jr., Executive Director, Assembly of Life Sciences

July 8 - 9, 1975 - (July 9)

Committee Members

Albert, Dr. Roy E., New York University Medical Center, New York, N.Y.—Chairman

Alpen, Dr. Edward L., Battelle Pacific Northwest Laboratory, Richland, Wash.

Bair, Dr. William J., Battelle Pacific Northwest Laboratory, Richland, Wash.

Casarett, Dr. George W., University of Rochester Medical Center, Rochester, N.Y.

Epp, Dr. Edward R., Massachusetts General Hospital, Boston, Mass.

Goldman, Dr. Marvin, University of California, Davis, Calif.

Gregg, Dr. Earle C., University Hospital, Cleveland, Ohio

Lewis, Dr. Edward B., California Institute of Technology, Pasadena, Calif.

Radford, Dr. Edward P., Johns Hopkins University, Baltimore, Maryland

Guest

Ellett, Dr. William H., Environmental Protection Agency, Washington, D.C.

National Academy of Sciences—Assembly of Life Sciences—Division of Medical Sciences

Hilberg, Dr. Albert W., Senior Staff Officer

November 21, 1975

Committee Members

Albert, Dr. Roy E., New York University Medical Center, New York, N.Y.—Chairman

Alpen, Dr. Edward L., Donner Laboratory, University of California, Berkeley, Calif.

Bair, Dr. William J., Battelle Pacific Northwest Laboratory, Richland, Wash.

Casarett, Dr. George W., University of Rochester Medical Center, Rochester, N.Y.

Epp, Dr. Edward R., Massachusetts General Hospital, Boston, Mass.

Goldman, Dr. Marvin, University of California, Davis, Calif.

Gregg, Dr. Earle C., University Hospital, Cleveland, Ohio

Lewis, Dr. Edward B., California Institute of Technology, Pasadena, Calif.

McClellan, Dr. Roger O., Lovelace Foundation, Albuquerque, New Mexico

Guest

Counts, Ms. Leila, Battelle Pacific Northwest Laboratory, Richland, Washington

National Academy of Sciences—Assembly of Life Sciences—Division of Medical Sciences

Hilberg, Dr. Albert W., Senior Staff Officer